4-CARBOX PYRAZOLE DERIVATIVES USEFUL AS ANTI-VIRAL AGENTS

FIELD OF THE INVENTION

The present invention relates to novel 4-carboxy pyrazole derivatives useful as anti-viral agents. Specifically, the present invention involves novel inhibitors of Hepatitis C Virus (HCV) replication.

BACKGROUND OF THE INVENTION

Infection with HCV is a major cause of human liver disease throughout the world. In the US, an estimated 4.5 million Americans are chronically infected with HCV. Although only 30% of acute infections are symptomatic, greater than 85% of infected individuals develop chronic, persistent infection. Treatment costs for HCV infection have been estimated at $5.46 billion for the US in 1997. Worldwide over 200 million people are estimated to be infected chronically. HCV infection is responsible for 40-60% of all chronic liver disease and 30% of all liver transplants. Chronic HCV infection accounts for 30% of all cirrhosis, end-stage liver disease, and liver cancer in the U.S. The CDC estimates that the number of deaths due to HCV will minimally increase to 38,000/year by the year 2010.

Due to the high degree of variability in the viral surface antigens, existence of multiple viral genotypes, and demonstrated specificity of immunity, the development of a successful vaccine in the near future is unlikely. Alpha-interferon (alone or in combination with ribavirin) has been widely used since its approval for treatment of chronic HCV infection. However, adverse side effects are commonly associated with this treatment: flu-like symptoms, leukopenia, thrombocytopenia, depression from interferon, as well as anemia induced by ribavirin (Lindsay, K.L. (1997) Hepatology 26 (suppl 1): 71S-77S). This therapy remains less effective against infections caused by HCV genotype 1 (which constitutes ~75% of all HCV infections in the developed markets) compared to infections caused by the other 5 major HCV genotypes. Unfortunately, only ~50-80% of the patients respond to this treatment (measured by a reduction in serum HCV RNA levels and normalization of liver enzymes) and, of responders, 50-70% relapse within 6 months of cessation of treatment. Recently, with the introduction of pegylated interferon (Peg-IFN), both initial and sustained response rates have improved substantially, and combination treatment of Peg-IFN with ribavirin constitutes the gold standard for therapy. However, the side effects associated with combination therapy and the impaired response in patients with genotype 1 present opportunities for improvement in the management of this disease.

First identified by molecular cloning in 1989 (Choo, Q-L et al (1989) Science 244:359-362), HCV is now widely accepted as the most common causative agent of post-transfusion non A, non-B hepatitis (NANBH) (Kuo, G et al (1989) Science 244:362-364). Due to its genome structure and sequence homology, this virus was assigned as a new genus in the *Flaviviridae* family. Like the other members of the *Flaviviridae,* such as flaviviruses (e.g. yellow fever virus and Dengue virus types 1-4) and pestiviruses (e.g. bovine viral diarrhea

virus, border disease virus, and classic swine fever virus) (Choo, Q-L et al (1989) Science 244:359-362; Miller, R.H. and R.H. Purcell (1990) Proc. Natl. Acad. Sci. USA 87:2057-2061), HCV is an enveloped virus containing a single strand RNA molecule of positive polarity. The HCV genome is approximately 9.6 kilobases (kb) with a long, highly conserved, noncapped 5' nontranslated region (NTR) of approximately 340 bases which functions as an internal ribosome entry site (IRES) (Wang CY et al 'An RNA pseudoknot is an essential structural element of the internal ribosome entry site located within the hepatitis C virus 5' noncoding region' RNA- A Publication of the RNA Society. 1(5): 526-537, 1995 Jul.). This element is followed by a region which encodes a single long open reading frame (ORF) encoding a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins.

Upon entry into the cytoplasm of the cell, this RNA is directly translated into a polypeptide of ~3000 amino acids comprising both the structural and nonstructural viral proteins. This large polypeptide is subsequently processed into the individual structural and nonstructural proteins by a combination of host and virally-encoded proteinases (Rice, C.M. (1996) in B.N. Fields, D.M.Knipe and P.M. Howley (eds) Virology 2nd Edition, p931-960; Raven Press, N.Y.). Following the termination codon at the end of the long ORF, there is a 3' NTR which roughly consists of three regions: an ~ 40 base region which is poorly conserved among various genotypes, a variable length poly(U)/polypyrimidine tract, and a highly conserved 98 base element also called the "3' X-tail" (Kolykhalov, A. et al (1996) J. Virology 70:3363-3371; Tanaka, T. et al (1995) Biochem Biophys. Res. Commun. 215:744-749; Tanaka, T. et al (1996) J. Virology 70:3307-3312; Yamada, N. et al (1996) Virology 223:255-261). The 3' NTR is predicted to form a stable secondary structure which is essential for HCV growth in chimps and is believed to function in the initiation and regulation of viral RNA replication.

The NS5B protein (591 amino acids, 65 kDa) of HCV (Behrens, S.E. et al (1996) EMBO J. 15:12-22), encodes an RNA-dependent RNA polymerase (RdRp) activity and contains canonical motifs present in other RNA viral polymerases. The NS5B protein is fairly well conserved both intra-typically (~95-98% amino acid (aa) identity across 1b isolates) and inter-typically (~85% aa identity between genotype 1a and 1b isolates). The essentiality of the HCV NS5B RdRp activity for the generation of infectious progeny virions has been formally proven in chimpanzees (A. A. Kolykhalov *et al.*. (2000) Journal of Virology, 74(4): 2046-2051). Thus, inhibition of NS5B RdRp activity (inhibition of RNA replication) is predicted to be useful to treat HCV infection.

Based on the foregoing, there exists a significant need to identify synthetic or biological compounds for their ability to inhibit HCV.

WO0102385 discloses certain 4-pyrazolyl quinoline derivatives having plant fungicidal activity.

WO0066562 discloses certain pyrazole derivatives having cyclooxygenase-2 inhibiting activity.

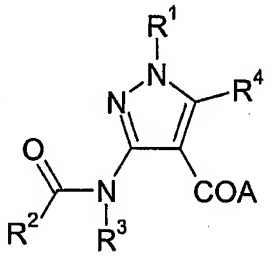
WO9600218 discloses certain pyrazole derivatives having PDE IV inhibiting activity.

SUMMARY OF THE INVENTION

The present invention involves novel 4-carboxy pyrazole compounds represented hereinbelow, pharmaceutical compositions comprising such compounds and use of the compounds in treating viral infection, especially HCV infection.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides at least one chemical entity chosen from compounds of Formula (I) :



(I)

wherein:
A represents hydroxy;

R^1 represents aryl, heteroaryl bonded through a ring carbon atom, or heterocyclyl bonded through a ring carbon atom, each of which may be optionally substituted by one or more substituents selected from -C_{1-6}alkyl, halo, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -$NR^EC(O)R^D$, -$NR^ECO_2R^D$, -$NR^EC(O)NR^FR^G$, -$SO_2NR^FR^G$, -SO_2R^D, nitro, cyano, -CF_3, -OCF_3, $NR^ESO_2R^D$, phenyl and heterocyclyl, wherein the -C_{1-6}alkyl substituent itself may be optionally substituted by one or more substituents selected from -C_{5-9}cycloalkyl, halo, -NR^BR^C, -$C(O)NR^BR^C$, -$NR^EC(O)R^D$, -SR^A, -SO_2R^D, -OR^A, oxo, phenyl, heteroaryl or heterocyclyl; or R^1 represents -C_{1-6}alkyl or -C_{5-9}cycloalkyl;

R^2 represents phenyl substituted by one or more substituents selected from -C_{1-6}alkyl, halo, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -$NR^EC(O)R^D$, -$NR^ECO_2R^D$, -$NR^EC(O)NR^FR^G$, -$SO_2NR^FR^G$, -SO_2R^D, nitro, cyano, and heterocyclyl; or R^2 represents -$(CH_2)_nC_{5-7}$cycloalkyl optionally substituted on the cycloalkyl by one or more substitutents selected from -C_{1-6}alkyl, =$CH(CH_2)_tH$, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -$NR^EC(O)R^D$, -$NR^ECO_2R^D$, -$NR^EC(O)NR^FR^G$, -$SO_2NR^FR^G$, -SO_2R^D, fluoro, nitro, cyano, oxo, and heterocyclyl, or wherein two substituents may together form a C_{1-2}alkylene bridge substituent;

t represents 0, 1, 2, 3 or 4;

n represents 0 or 1;

R^3 represents heterocyclyl or heteroaryl; or phenyl optionally substituted by one or more substituents selected from $-C_{1-6}$alkyl, halo, $-OR^A$, $-SR^A$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^EC(O)R^D$, $-NR^ECO_2R^D$, $-NR^EC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, nitro, cyano, and heterocyclyl; or R^3 represents $-C_{1-6}$alkyl optionally substituted by one or more substituents selected from $-C_{1-6}$alkyl, $-OR^A$, $-SR^A$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^EC(O)R^D$, $-NR^ECO_2R^D$, $-NR^EC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, fluoro, nitro, cyano, oxo, phenyl, heteroaryl and heterocyclyl;

R^4 represents hydrogen;

R^A represents hydrogen, $-C_{1-6}$alkyl, arylalkyl, heteroarylalkyl, aryl, heterocyclyl or heteroaryl;

R^B and R^C independently represent hydrogen, $-C_{1-6}$alkyl, aryl, heterocyclyl or heteroaryl; or R^B and R^C together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R^D is selected from the group consisting of $-C_{1-6}$alkyl, aryl, heterocyclyl, heteroaryl, arylalkyl, and heteroarylalkyl;

R^E represents hydrogen or $-C_{1-6}$alkyl;

R^F and R^G are independently selected from the group consisting of hydrogen, $-C_{1-6}$alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R^F and R^G together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

and salts, solvates and esters thereof.

There is provided as a further aspect of the present invention at least one chemical entity chosen from compounds of Formula (I) and physiologically acceptable salts, solvates and esters thereof for use in human or veterinary medical therapy, particularly in the treatment or prophylaxis of viral infection, particularly HCV infection.

It will be appreciated that reference herein to therapy and/or treatment includes, but is not limited to prevention, retardation, prophylaxis, therapy and cure of the disease. It will further be appreciated that references herein to treatment or prophylaxis of HCV infection includes

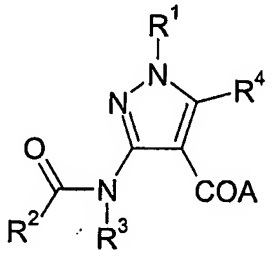
treatment or prophylaxis of HCV-associated disease such as liver fibrosis, cirrhosis and hepatocellular carcinoma.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with viral infection, particularly HCV infection, which method comprises administering to said human or animal subject an effective amount of at least one chemical entity chosen from compounds of Formula (I) and physiologically acceptable salts, solvates and esters thereof.

According to another aspect of the invention, there is provided the use of at least one chemical entity chosen from compounds of Formula (I) and physiologically acceptable salts, solvates and esters thereof in the manufacture of a medicament for the treatment and/or prophylaxis of viral infection, particularly HCV infection.

It will be appreciated that the chemical entities of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic, diastereoisomeric, and optically active forms. All of these racemic compounds, enantiomers and diastereoisomers are contemplated to be within the scope of the present invention.

In one aspect, the present invention provides at least one chemical entity chosen from compounds of Formula (Ia) :



(Ia)

wherein:

A represents hydroxy;

R^1 represents aryl, heteroaryl bonded through a ring carbon atom, heterocyclyl bonded through a ring carbon atom, each optionally substituted by $Q\text{-}R^5$; or R^1 represents $-CH{=}CHR^6$, $-C_{1\text{-}6}$alkyl, or $-C_{5\text{-}9}$cycloalkyl;

R^2 represents phenyl substituted by one or more substituents selected from $-C_{1\text{-}6}$alkyl, halo, $-OR^A$, $-SR^A$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^EC(O)R^D$, $-NR^ECO_2R^D$, $-NR^EC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, nitro, cyano, oxo, and heterocyclyl; or R^2 represents $-(CH_2)_nC_{5\text{-}7}$cycloalkyl optionally substituted on the cycloalkyl by one or more substitutents selected from $-C_{1\text{-}6}$alkyl, $-OR^A$, $-SR^A$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^EC(O)R^D$, $-NR^ECO_2R^D$, $-NR^EC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, fluoro, nitro, cyano, oxo,

and heterocyclyl, or wherein two substituents may together form a C_{1-2}alkylene bridge substituent;

n represents 0 or 1;

R^3 represents heterocyclyl or heteroaryl; or phenyl optionally substituted by one or more substituents selected from -C_{1-6}alkyl, halo, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -$NR^EC(O)R^D$, -$NR^ECO_2R^D$, -$NR^EC(O)NR^FR^G$, -$SO_2NR^FR^G$, -SO_2R^D, nitro, cyano, oxo, and heterocyclyl; or R^3 represents -C_{1-6}alkyl optionally substituted by one or more substituents selected from -C_{1-6}alkyl, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -$NR^EC(O)R^D$, -$NR^ECO_2R^D$, -$NR^EC(O)NR^FR^G$, -$SO_2NR^FR^G$, -SO_2R^D, fluoro, nitro, cyano, oxo, phenyl, heteroaryl and heterocyclyl;

R^4 represents hydrogen or unsubstituted -C_{1-4}alkyl;

R^5 represents aryl, heteroaryl or heterocyclyl;

R^6 represents methylpropyl, *n*-butyl or cyclohexyl, or phenyl optionally substituted by fluoro;

R^7 represents C_{1-3}alkyl, aryl, heteroaryl or heterocyclyl;

Q represents -C_{2-4}alkenylene-, -C_{1-4}alkylene-, -O-C_{1-4}alkylene- or -C_{1-4}alkylene-O- wherein each -C_{2-4}alkenyl- and -C_{1-4}alkylene- may be optionally substituted by -$S(O)_mR^7$;

m represents 0, 1 or 2;

R^A represents hydrogen, -C_{1-6}alkyl, arylalkyl, heteroarylalkyl, aryl or heteroaryl;

R^B and R^C independently represent hydrogen, -C_{1-6}alkyl, aryl or heteroaryl; or R^B and R^C together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

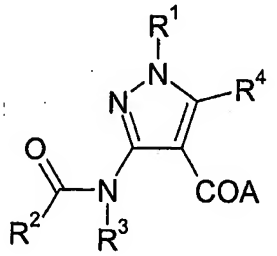
R^D is selected from the group consisting of -C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R^E represents hydrogen or -C_{1-6}alkyl;

R^F and R^G are independently selected from the group consisting of hydrogen, -C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R^F and R^G together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

and salts, solvates and esters thereof.

In a further aspect, the present invention provides at least one chemical entity chosen from compounds of Formula (Ib) :



(Ib)

wherein:

A represents hydroxy;

R^1 represents aryl, heteroaryl bonded through a ring carbon atom, heterocyclyl bonded through a ring carbon atom, or C_{1-6}alkyl;

R^2 represents phenyl substituted by one or more substituents selected from C_{1-6}alkyl, halo, OR^A, SR^A, $C(O)NR^BR^C$, $C(O)R^D$, CO_2H, CO_2R^D, NR^BR^C, $NR^EC(O)R^D$, $NR^ECO_2R^D$, $NR^EC(O)NR^FR^G$, $SO_2NR^FR^G$, SO_2R^D, nitro, cyano, oxo, and heterocyclyl; or R^2 represents $-(CH_2)_nC_{5-7}$cycloalkyl optionally substituted on the cycloalkyl by one or more substitutents selected from C_{1-6}alkyl, OR^A, SR^A, $C(O)NR^BR^C$, $C(O)R^D$, CO_2H, CO_2R^D, NR^BR^C, $NR^EC(O)R^D$, $NR^ECO_2R^D$, $NR^EC(O)NR^FR^G$, $SO_2NR^FR^G$, SO_2R^D, fluoro, nitro, cyano, oxo, and heterocyclyl, or wherein two substituents may together form a C_{1-2}alkylene bridge;

n represents 0 or 1;

R^3 represents heterocyclyl; or phenyl optionally substituted by one or more substituents selected from C_{1-6}alkyl, halo, OR^A, SR^A, $C(O)NR^BR^C$, $C(O)R^D$, CO_2H, CO_2R^D, NR^BR^C, $NR^EC(O)R^D$, $NR^ECO_2R^D$, $NR^EC(O)NR^FR^G$, $SO_2NR^FR^G$, SO_2R^D, nitro, cyano, oxo, and heterocyclyl; or R^3 represents C_{1-6}alkyl optionally substituted by one or more substituents selected from C_{1-6}alkyl, OR^A, SR^A, $C(O)NR^BR^C$, $C(O)R^D$, CO_2H, CO_2R^D, NR^BR^C, $NR^EC(O)R^D$, $NR^ECO_2R^D$, $NR^EC(O)NR^FR^G$, $SO_2NR^FR^G$, SO_2R^D, fluoro, nitro, cyano, oxo, phenyl, heteroaryl and heterocyclyl;

R^4 represents hydrogen or unsubstituted C_{1-4}alkyl;

R^A represents hydrogen, C_{1-6}alkyl, arylalkyl, heteroarylalkyl, aryl or heteroaryl;

R^B and R^C independently represent hydrogen, C_{1-6}alkyl, aryl or heteroaryl; or R^B and R^C together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

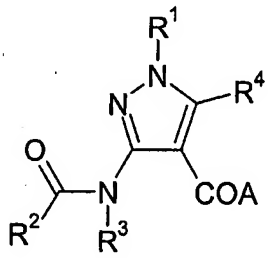
R^D is selected from the group consisting of C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

R^E represents hydrogen or C_{1-6}alkyl;

R^F and R^G are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl; or R^F and R^G together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

and salts, solvates and esters thereof.

In a further aspect, the present invention provides at least one chemical entity chosen from compounds of Formula (Ic) :



(Ic)

wherein:
A represents hydroxy;

R^1 represents aryl, heteroaryl bonded through a ring carbon atom, heterocyclyl bonded through a ring carbon atom, each optionally substituted by Q-R^5; or R^1 represents -C_{5-7}cycloalkyl or -CH=CHR^6;

R^2 represents -$(CH_2)_nC_{5-7}$cycloalkyl optionally substituted on the cycloalkyl by one or more substitutents selected from -C_{1-6}alkyl, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -SO_2R^D, fluoro, cyano, and oxo; or R^2 represents phenyl optionally substituted by one or more substituents selected from -C_{1-6}alkyl and halo;

n represents 0 or 1;

R^3 represents heterocyclyl; or phenyl optionally substituted by one or more substituents selected from -C_{1-6}alkyl, halo, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -SO_2R^D, nitro, cyano, oxo, and heterocyclyl; or R^3 represents -C_{1-6}alkyl optionally substituted by one or more substituents selected from -C_{1-6}alkyl, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -SO_2R^D, fluoro, cyano, oxo, phenyl, heteroaryl and heterocyclyl;

R^4 represents hydrogen or unsubstituted -C_{1-4}alkyl;

R^5 represents aryl, heteroaryl or heterocyclyl;

R^6 represents 2-methylpropyl, *n*-butyl or cyclohexyl, or phenyl optionally substituted by fluoro;

R^7 represents C_{1-3}alkyl, aryl, heteroaryl or heterocyclyl;

Q represents -C_{2-4}alkenylene-, -C_{1-4}alkylene-, -O-C_{1-4}alkylene- or -C_{1-4}alkylene-O- wherein each -C_{2-4}alkenyl- and -C_{1-4}alkylene- may be optionally substituted by -$S(O)_mR^7$;

m represents 0, 1 or 2;

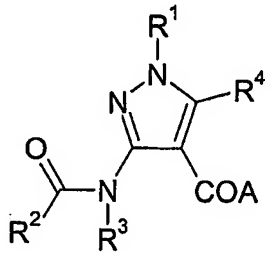
R^A represents hydrogen, -C_{1-6}alkyl, arylalkyl, heteroarylalkyl, aryl or heteroaryl;

R^B and R^C independently represent hydrogen, -C_{1-6}alkyl, aryl or heteroaryl; or R^B and R^C together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R^D is selected from the group consisting of C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

and salts, solvates and esters thereof.

In a further aspect, the present invention provides at least one chemical entity chosen from compounds of Formula (Id) :



(Id)

wherein:
A represents hydroxy;

R^1 represents aryl, heteroaryl bonded through a ring carbon atom, or heterocyclyl bonded through a ring carbon atom;

R^2 represents $-(CH_2)_nC_{5-7}$cycloalkyl optionally substituted on the cycloalkyl by one or more substitutents selected from C_{1-6}alkyl, OR^A, SR^A, $C(O)NR^BR^C$, $C(O)R^D$, CO_2H, CO_2R^D, NR^BR^C, SO_2R^D, fluoro, cyano, and oxo;

n represents 0 or 1;

R^3 represents heterocyclyl; or phenyl optionally substituted by one or more substituents selected from C_{1-6}alkyl, halo, OR^A, SR^A, $C(O)NR^BR^C$, $C(O)R^D$, CO_2H, CO_2R^D, NR^BR^C, SO_2R^D, nitro, cyano, oxo, and heterocyclyl; or R^3 represents C_{1-6}alkyl optionally substituted by one or more substituents selected from C_{1-6}alkyl, OR^A, SR^A, $C(O)NR^BR^C$, $C(O)R^D$, CO_2H, CO_2R^D, NR^BR^C, SO_2R^D, fluoro, cyano, oxo, phenyl, heteroaryl and heterocyclyl;

R^4 represents hydrogen or unsubstituted C_{1-4}alkyl;

R^A represents hydrogen, C_{1-6}alkyl, arylalkyl, heteroarylalkyl, aryl or heteroaryl;

R^B and R^C independently represent hydrogen, C_{1-6}alkyl, aryl or heteroaryl; or R^B and R^C together with the nitrogen atom to which they are attached form a 5 or 6 membered saturated cyclic group;

R^D is selected from the group consisting of C_{1-6}alkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl;

and salts, solvates and esters thereof.

It will be appreciated that the following aspects may apply, where appropriate to compounds of Formula (I), (Ia), (Ib), (Ic) and (Id).

In one aspect, R^1 represents phenyl, heteroaryl bonded through a ring carbon atom, or heterocyclyl bonded through a ring carbon atom, each of which may be optionally substituted by one or more substituents selected from -C_{1-6}alkyl, halo, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -$NR^EC(O)R^D$, -SO_2R^D, cyano, -CF_3, -OCF_3, $NR^ESO_2R^D$, phenyl and heterocyclyl, wherein the -C_{1-6}alkyl substituent itself may be optionally substituted by one or more substituents selected from -C_{5-9}cycloalkyl, halo, -NR^BR^C, -$C(O)NR^BR^C$, -$NR^EC(O)R^D$, -SR^A, -SO_2R^D, OR^A, phenyl, heteroaryl or heterocyclyl; or R^1 represents -C_{1-6}alkyl or -C_{5-9}cycloalkyl (in another aspect optionally substituted cyclohexenyl).

In a further aspect, R^1 represents a substituent selected from phenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 4-acetylphenyl, 4-(acetylamino)phenyl, 4-aminophenyl, 4-(dimethylamino)phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-(trifluoromethoxy)phenyl, 4-(trifluoromethoxy)phenyl, 3-cyanophenyl, 4-cyanophenyl, 4-[(dimethylamino)carbonyl]phenyl, 3,5-dimethylphenyl, 3-chloro-5-fluorophenyl, 3-chloro-4-benzyloxyphenyl, 3,5-bis-(trifluoromethyl)phenyl, 1,3-benzodioxol-5-yl, 2,3-dihydro-1-benzofuran-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1H-indol-5-yl, indol-6-yl, benzofuran-6-yl, 3,4,5-trifluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-methylsulfonylphenyl, 4-(phenylthiomethyl)phenyl, 4-

[(phenylsulfonyl)amino]phenyl, 3-methylphenyl, 4-methylphenyl, 4-chloro-3-fluoro-phenyl, 4-chloro-3-methylphenyl, 3-amino-4-methylphenyl, 3-fluoro-4-methylphenyl, 3,4-di-fluorophenyl, 4-biphenylyl, 4-(phenylsulfonylmethyl)phenyl, 4-[(phenoxy)methyl]phenyl, 4-(phenoxy)phenyl, 4-[(1,3-thiazol-4-ylmethyl)oxy]phenyl, 4-[(E/Z)-2-phenylethenyl]phenyl, 4-(2-phenylethyl)phenyl, 4-[(1,3-thiazol-4-yl)ethyl]phenyl, 4-[(1,3-thiazol-2-yl)ethyl]phenyl, 4-[2-(1H-pyrazol-3-yl)ethyl]phenyl, (E)-2-*tert*-butylethenyl, (E)-hexen-1-yl, (E)-2-cyclohexylethenyl, cyclohexyl, 4-(2-cyclohexylethyl)phenyl, cyclohexen-1-yl, cyclohepten-1-yl, 4-methyl-1-cyclohexen-1-yl, 4-trifluoromethylcyclohexen-1-yl, 4-benzyloxycyclohexen-1-yl, (4,4-dimethyl)cyclohexen-1-yl, (E)-4-methyl-1-penten-1-yl, (E)-2-phenylethenyl, 4-[(E)-2-(cyclohexyl)ethenyl]phenyl, 4-[(E)-2-phenylethenyl]phenyl, 4-[(Z)-2-phenylethenyl]phenyl, 4-[(E)-phenyl-2-methylethenyl]phenyl, 4-[(E)-2-(3-pyrazolyl)-ethenyl]phenyl, 4-[(Z)-2-(3-pyrazolyl)ethenyl]phenyl, 4-[(E)-(pyridine-4-yl)ethenyl]phenyl, 4-[2-(pyridin-2-yl)ethenyl]-phenyl, 4-[2-(pyridin-2-yl)ethyl]phenyl, 4-[(E)-2-(tetrahydro-2H-pyran-4-yl)ethenyl]phenyl, 4-[(E/Z)-(1,3-thiazol-2-yl)ethenyl]phenyl, 4-[(E)-(1,3-thiazol-4-yl)ethenyl]phenyl, 4-[(Z)-(1,3-thiazol-4-yl)ethenyl]phenyl, 4-[(E)-(2-methyl-1,3-thiazol-4-yl)ethenyl]phenyl, 4-[(E)-(furan-2-yl)ethenyl]phenyl, (E)-2-(4-fluorophenyl)ethenyl, 4-ethenylphenyl, 4-(hydroxymethyl)phenyl, 4-ethylphenyl, 4-(1-methylethyl)phenyl, 3-thienyl, 5-acetyl-2-thienyl, 5-chloro-2-thienyl, 5-methyl-2-thienyl, 5-phenyl-2-thienyl, 1-(methylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl, 4-[(phenylamino)carbonyl]phenyl, 4-{[(4-fluorophenyl)amino]carbonyl}phenyl, 4-[(phenyl-carbonyl)amino]phenyl, 4-[(3-methylphenylcarbonyl)amino]phenyl, 4-[(3-chlorophenyl-carbonyl)amino]phenyl, 4-[(4-fluorophenylcarbonyl)amino]phenyl, and 4-[(cyclohexylcarbonyl)-amino]phenyl.

In a further aspect, R^1 represents a substituent selected from phenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 4-acetylphenyl, 4-(acetylamino)phenyl, 4-aminophenyl, 4-(dimethylamino)phenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-(trifluoromethoxy)phenyl, 4-(trifluoromethoxy)phenyl, 3-cyanophenyl, 4-cyanophenyl, 4-[(dimethylamino)carbonyl]phenyl, 3,5-dimethylphenyl, 3-chloro-5-fluorophenyl, 3,5-bis-(trifluoromethyl)phenyl, 1,3-benzodioxol-5-yl, 2,3-dihydro-1-benzofuran-5-yl, 2,3-dihydro-1,4-benzodioxan-6-yl, 1H-indol-5-yl, 3,4,5-trifluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-methylsulfonylphenyl, 3-methylphenyl, 4-methylphenyl, 3-fluoro-4-chlorophenyl, 3-methyl-4-chlorophenyl, 3-amino-4-methylphenyl, 3-fluoro-4-methylphenyl, 3,4-di-fluorophenyl, 4-biphenylyl, 4-[(phenylmethyl)oxy]phenyl, 4-[(E/Z)-2-phenylethenyl]phenyl, 4-(2-phenylethyl)phenyl, (E)-hexen-1-yl, (E)-2-cyclohexylethenyl, cyclohexyl, cyclohexen-1-yl, 4-methyl-1-cyclohexen-1-yl, (E)-4-methyl-1-penten-1-yl, (E)-2-phenylethenyl, (E)-2-(4-fluorophenyl)ethenyl, 4-ethenylphenyl, 4-(hydroxymethyl)phenyl, 4-ethylphenyl, 4-isopropylphenyl, 3-thienyl, 5-acetyl-2-thienyl, 5-chloro-2-thienyl, 5-methyl-2-thienyl, 5-phenyl-2-thienyl, and 1-(methylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl.

In a further aspect, R^1 represents phenyl optionally substituted by one or more substituents selected from $-C_{1-6}$alkyl, halo, $-OR^A$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-NR^BR^C$, $-NR^EC(O)R^D$,

$-SO_2R^D$, cyano, $-CF_3$, $-OCF_3$, $NR^ESO_2R^D$, phenyl and heterocyclyl, wherein the $-C_{1-6}$alkyl substituent itself may be optionally substituted by $-C(O)NR^BR^C$, $-NR^EC(O)R^D$, $-SO_2R^D$, OR^A, phenyl, heteroaryl or heterocyclyl; or R^1 represents $-C_{5-6}$cycloalkyl.

In another aspect, R^1 is other than optionally substituted quinolin-4-yl.

In another aspect, R^1 is other than 4-$(S(O)_2R^D)$-phenyl or 4-(SR^A)-phenyl each of which is further substituted on the phenyl ring by at least one other substituent.

In another aspect, R^1 is other than a group which comprises phenyl substituted in each of the 3 and 4 positions by a substituent, which may be the same of different, selected from $-OR^A$ and $-SR^A$.

In one aspect, R^2 represents optionally substituted C_{5-7}cycloalkyl, especially C_{5-7}cycloalkyl substituted by C_{1-4}alkyl. In a further aspect, R^2 represents *trans*-4-methylcyclohexyl, cyclohexylmethyl, 4-methylphenyl, 4-bromo-2-chlorophenyl, 2-hydroxy-*trans*-4-methylcyclohexyl, 4-methylidenecyclohexyl, In another aspect, R^2 represents optionally substituted $-C_{5-6}$cycloalkyl. In yet another aspect R^2 represents $-C_6$cycloalkyl substituted by $-C_{1-4}$alkyl, especially *trans*-4-methylcyclohexyl.

In one aspect, R^3 represents unsubstituted $-C_{1-4}$alkyl, phenyl, [2-(dimethylamino)-2-oxoethyl], 4-piperidinyl, {1-[(methyloxy)carbonyl]-4-piperidinyl}, [1-(methylsulfonyl)-4-piperidinyl], 1-methyl-4-piperidinyl, {1-[(ethylamino)carbonyl]-4-piperidinyl, {1-[(tert-butyloxy)carbonyl]-4-piperidinyl}, 2-pyrazinylmethyl, phenylmethyl, cyclopentyl, tetrahydro-2H-pyran-4-yl, tetrahydro-3-furanyl, [1-acetyl-4-piperidinyl]. In a further aspect, R^3 represents unsubstituted $-C_{1-4}$alkyl, phenyl, [2-(dimethylamino)-2-oxoethyl], {1-[(methyloxy)carbonyl]-4-piperidinyl}, [1-(methylsulfonyl)-4-piperidinyl], 1-methyl-4-piperidinyl, {1-[(ethylamino)carbonyl]-4-piperidinyl, 2-pyrazinylmethyl, phenylmethyl, cyclopentyl, tetrahydro-2H-pyran-4-yl, tetrahydro-3-furanyl, [1-acetyl-4-piperidinyl]. In another aspect R^3 represents unsubstituted C_{1-4}alkyl. In a further aspect, R^3 represents 1-methylethyl, tetrahydro-2H-pyran-4-yl, tetrahydro-3-furanyl or [1-(methylsulfonyl)-4-piperidinyl].

In one aspect, R^4 represents hydrogen.

It is to be understood that the present invention covers all combinations of aspects, suitable, convenient and preferred groups described herein.

As used herein, "acetyl" refers to $-C(O)CH_3$.

As used herein, "acetylamino" refers to $-N(H)C(O)CH_3$.

As used herein unless otherwise specified, "alkyl" refers to an optionally substituted hydrocarbon group. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. Where the alkyl group is linear or branched, examples of such groups include methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl or hexyl and the like. Where the alkyl hydrocarbon group is unsaturated, it will be understood that there will be a minimum of 2 carbon atoms in the group, for example an alkenyl or alkynyl group. Where the alkyl hydrocarbon group is cyclic, it will be understood that there will be a minimum of 3 carbon atoms in the group. In one aspect, alkyl moieties are -C_{1-4}alkyl. Unless otherwise stated, optional substituents include -C_{1-6}alkyl (unsubstituted), =$CH(CH_2)_tH$, fluoro, -CF_3, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -$NR^EC(O)R^D$, -$NR^ECO_2R^D$, -$NR^EC(O)NR^FR^G$, -$SO_2NR^FR^G$, -SO_2R^D, nitro, cyano, oxo, aryl, heteroaryl and heterocyclyl.

As used herein, the term "alkenyl" refers to a linear or branched hydrocarbon group containing one or more carbon-carbon double bonds. In one aspect the alkenyl group has from 2 to 6 carbon atoms. Examples of such groups include ethenyl, propenyl, butenyl, pentenyl or hexenyl and the like.

As used herein, the term "alkynyl" refers to a linear or branched hydrocarbon group containing one or more carbon-carbon triple bonds. In one aspect the alkynyl group has from 2 to 6 carbon atoms. Examples of such groups include ethynyl, propynyl, butynyl, pentynyl or hexynyl and the like.

As used herein unless otherwise specified, "cycloalkyl" refers to an optionally substituted, cyclic hydrocarbon group. The hydrocarbon group may be saturated or unsaturated, monocyclic or bridged bicyclic. Where the cycloalkyl group is saturated, examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like. Where the cycloalkyl group is unsaturated, examples of such groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl or cyclooctenyl and the like. In one aspect, the cycloalkyl group has from 5 to 7 carbon atoms. In one aspect, cycloalkyl moieties are cyclohexenyl, cyclopentenyl and cyclohexyl. Unless otherwise stated, the cycloalkyl group may be substituted by one or more optional substituents including -C_{1-6}alkyl (unsubstituted), =$CH(CH_2)_tH$, fluoro, -CF_3, -OR^A, -SR^A, -$C(O)NR^BR^C$, -$C(O)R^D$, -CO_2H, -CO_2R^D, -NR^BR^C, -$NR^EC(O)R^D$, -$NR^ECO_2R^D$, -$NR^EC(O)NR^FR^G$, -$SO_2NR^FR^G$, -SO_2R^D, nitro, cyano, oxo, phenyl and heterocyclyl.

As used herein, the term " alkoxy" refers to an -O-alkyl group wherein alkyl is as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, pentoxy or hexoxy and the like.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring

systems. "Aryl" includes carbocyclic aryl and biaryl groups, all of which may be optionally substituted. In one aspect, "aryl" moieties contain 6-10 carbon atoms. In one aspect, "aryl" moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted phenyl. In one aspect, unless otherwise stated, "aryl" substituents are selected from the group consisting of $-C_{1-6}$alkyl, halo, $-OR^A$, $-SR^A$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^EC(O)R^D$, $-NR^ECO_2R^D$, $-NR^EC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, nitro, cyano, heterocyclyl, $-CF_3$, $-OCF_3$ and phenyl.

As used herein, "arylalkyl" refers to an aryl group attched to the parent molecular moiety through an alkyl group.

As used herein, "carbonyl" refers to -C(O)-.

As used herein, "cyano" refers to -CN.

As used herein, "halogen" or "halo" refer to a fluorine, chlorine, bromine or iodine atom. References to "fluoro", "chloro", "bromo" or "iodo" should be construed accordingly.

As used herein, "heteroaryl" refers to an optionally substituted, 5, 6, 8, 9 or 10 membered, aromatic group comprising one to four heteroatoms selected from N, O and S, with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. In one aspect, "heteroaryl" moieties are unsubstituted, monosubstituted, disubstituted or trisubstituted (where applicable) pyridyl, pyrazinyl, thiazolyl, thienyl, benzodioxolyl, benzofuranyl, benzodioxinyl and indolyl. In one aspect, unless otherwise stated, "heteroaryl" substituents are selected from the group consisting of $-C_{1-6}$alkyl, halo, $-OR^A$, $-SR^A$, $-C(O)NR^BR^C$, $-C(O)R^D$, $-CO_2H$, $-CO_2R^D$, $-NR^BR^C$, $-NR^EC(O)R^D$, $-NR^ECO_2R^D$, $-NR^EC(O)NR^FR^G$, $-SO_2NR^FR^G$, $-SO_2R^D$, nitro, cyano, heterocyclyl, $-CF_3$ and phenyl.

As used herein, "heteroarylalkyl" refers to a heteroaryl group attched to the parent molecular moiety through an alkyl group.

As used herein, "heterocyclic" and "heterocyclyl" refer to an optionally substituted, 5 or 6 membered, saturated or partially saturated, cyclic group containing 1 or 2 heteroatoms selected from N, optionally substituted by hydrogen, $-C_{1-6}$alkyl, $-C(O)R^D$, $-C(O)NR^BR^C$, $-C(O)OR^4$, $-SO_2R^D$, aryl or heteroaryl; O; and S, optionally substituted by one or two oxygen atoms. Ring carbon atoms may be optionally substituted by $-C_{1-6}$alkyl, $-C(O)R^D$, or $-SO_2R^D$. In one aspect, unless otherwise stated, "heterocyclic" moieties are unsubstituted or monosubstituted tetrahydro-2H-pyran-4-yl, piperidinyl and 1,2,3,6-tetrahydro-4-pyridinyl.

As used herein, "nitro" refers to $-NO_2$.

As used herein, "oxo" refers to =O.

As used herein, "Ac" refers to "acetyl", "Et" refers to "ethyl", "iPr" refers to "isopropyl", "Me" refers to "methyl", "OBn" refers to "benzyloxy", and "Ph" refers to "phenyl".

In one aspect, chemical entities useful in the present invention may be chosen from compounds of Formula (I) selected from the group consisting of:
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-phenyl-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(4-methylphenyl)-1H-pyrazole-4-carboxylic acid;
1-(1-Cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Chloro-3-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(6-Indolyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Hydroxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-[4-(Acetylamino)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Biphenylyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-(Dimethylamino)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(methyloxy)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(4-Acetylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(trifluoromethyl)oxy]phenyl}-1H-pyrazole-4-carboxylic acid;
1-(4-Cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-{4-[(Dimethylamino)carbonyl]phenyl}-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3-thienyl)-1H-pyrazole-4-carboxylic acid;

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(3,5-Dimethylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Chloro-5-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[3,5-Bis(trifluoromethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(1,3-Benzodioxol-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(2,3-Dihydro-1-benzofuran-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3,4,5-trifluorophenyl)-1H-pyrazole-4-carboxylic acid;
1-(4-Chlorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[3-(methyloxy)phenyl]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(methylsulfonyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(2-Fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Hydroxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3-methylphenyl)-1H-pyrazole-4-carboxylic acid;
1-(3-Fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Aminophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Chlorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{3-[(trifluoromethyl)oxy]phenyl}-1H-pyrazole-4-carboxylic acid;
1-(4-Chloro-3-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Amino-4-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Fluoro-4-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;

1-(3,4-Difluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[(E)-1-Hexen-1-yl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[(E)-2-Cyclohexylethenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[(E)-4-methyl-1-penten-1-yl]-1H-pyrazole-4-carboxylic acid;
1-[(E)-2-(4-Fluorophenyl)ethenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Ethenylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-(Hydroxymethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Ethylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(1-methylethyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(5-Acetyl-2-thienyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(5-Chloro-2-thienyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(5-methyl-2-thienyl)-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(5-phenyl-2-thienyl)-1H-pyrazole-4-carboxylic acid;
1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylic acid;
1-(6-Benzofuranyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(Cyclohepten-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylic acid;
1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-(methylsulfonyl)-4-piperidinyl]amino]-1H-pyrazole-4-carboxylic acid;
1-((4,4-Dimethyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Chloro-4-benzyloxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Benzyloxy-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1)-1H-pyrazole-4-carboxylic acid;
1-(4,4-Dimethyl)cyclohexen-1-yl)-3-{[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino}-1H-pyrazole-4-carboxylic acid;

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(E)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(Z)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(Z)-2-(3-pyrazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(E)-2-(3-pyrazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(E)-2-(tetrahydro-2H-pyran-4-yl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(E)-2-(4-thiazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(Z)-2-(4-thiazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
1-((E)-2-*tert*-Butyl-ethenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-((E)-2-Phenyl-ethenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Methyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-{(1-Methylethyl)[(4-methylidenecyclohexyl)carbonyl]amino}-1-phenyl-1*H*-pyrazole-4-carboxylic acid;
1-(4-Trifluoromethyl-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenyloxy)methyl]phenyl}-1*H*-pyrazole-4-carboxylic acid;
1-[4-(Phenylsulfonylmethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-(Phenylthiomethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-(Phenoxy)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-{(1,3-Thiazol-4-ylmethyl)oxy}phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-([E]-Phenylethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-[Z]-Phenylethenyl))phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-([E,Z]-(1,3-Thiazol-2-yl)ethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;

1-[4-([E]-Phenyl-2-methylethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-[E]-(Pyridin-4-yl)ethenyl))phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-([E]-(1,3-Thiazol-4-yl)ethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-([E]-(Furan-2-yl)ethenyl))phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-([E]-(2-Methyl-1,3-thiazol-4-yl)ethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[(Cyclohexylacetyl)(1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{(1-Methylethyl)[(4-methylphenyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(4-Bromo-2-chlorophenyl)carbonyl](1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](phenyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{[2-(Dimethylamino)-2-oxoethyl][(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-([(*trans*-4-Methylcyclohexyl)carbonyl]{1-[(methyloxy)carbonyl]-4-piperidinyl}amino)-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{[(*trans*-4-Methylcyclohexyl)carbonyl][1-(methylsulfonyl)-4-piperidinyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methyl-4-piperidinyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{{1-[(Ethylamino)carbonyl]-4-piperidinyl}[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](2-pyrazinylmethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
rel-3-[{[(1S,2R,4S)-2-Hydroxy-4-methylcyclohexyl]carbonyl}(1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(3-methoxyphenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylmethyl)oxy]phenyl}-1H-pyrazole-4-carboxylic acid;
1-(1H-Indol-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(2-phenylethyl)phenyl]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[2-phenylethyl]phenyl}-1H-pyrazole-4-carboxylic acid;

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-[(1,3-thiazol-4-yl)-ethyl]phenyl]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(1,3-thiazol-4-yl)-ethyl]phenyl}-1H-pyrazole-4-carboxylic acid;
1-Cyclohexyl-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[1-(methylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](phenylmethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{Cyclopentyl[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{(1-Acetyl-4-piperidinyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](4-piperidinyl)amino]-1-phenyl-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E)-2-cyclohexylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
1-[4-(2-Cyclohexylethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[2-pyridinylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[2-pyridinylethyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[1,3-thiazol-2-ylethyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[2-(1*H*-pyrazol-3-yl)ethyl]phenyl}-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylamino)carbonyl]phenyl}-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(3-methylphenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid;
3-([(*trans*-4-Methylcyclohexyl)carbonyl]{1-[(*tert*-butyloxy)carbonyl]-4-piperidinyl}amino)-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(4-fluorophenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid;

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(cyclohexylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid;
1-(4-{[(4-Fluorophenyl)amino]carbonyl}phenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{3-[(chlorophenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylsulfonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid;
1-(4-Methyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylic acid;
1-(4,4-Dimethyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-1*H*-pyrazole-4-carboxylic acid;
and salts, solvates and esters, and individual enantiomers thereof where appropriate.

In one aspect, chemical entities useful in the present invention may be chosen from compounds of Formula (I) selected from the group consisting of:
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-phenyl-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(4-methylphenyl)-1H-pyrazole-4-carboxylic acid;
1-(4-Hydroxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-[4-(Acetylamino)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Biphenylyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-(Dimethylamino)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(methyloxy)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(4-Acetylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(trifluoromethyl)oxy]phenyl}-1H-pyrazole-4-carboxylic acid;
1-(4-Cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-{4-[(Dimethylamino)carbonyl]phenyl}-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3-thienyl)-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(3,5-Dimethylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Chloro-5-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[3,5-Bis(trifluoromethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(1,3-Benzodioxol-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(2,3-Dihydro-1-benzofuran-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl) amino]-1H-pyrazole-4-carboxylic acid;
1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl) amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3,4,5-trifluorophenyl)-1H-pyrazole-4-carboxylic acid;
1-(4-Chlorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[3-(methyloxy)phenyl]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(methylsulfonyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(2-Fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Hydroxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3-methylphenyl)-1H-pyrazole-4-carboxylic acid;
1-(3-Fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Aminophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Chlorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{3-[(trifluoromethyl)oxy] phenyl}-1H-pyrazole-4-carboxylic acid;
1-(4-Chloro-3-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Chloro-3-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;

1-(3-Amino-4-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3-Fluoro-4-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(3,4-Difluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[(1E)-1-Hexen-1-yl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[(E)-2-Cyclohexylethenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[(1E)-4-methyl-1-penten-1-yl]-1H-pyrazole-4-carboxylic acid;
1-[(E)-2-(4-Fluorophenyl)ethenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl) amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Ethenylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-[4-(Hydroxymethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(4-Ethylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(1-methylethyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(5-Acetyl-2-thienyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-(5-Chloro-2-thienyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(5-methyl-2-thienyl)-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(5-phenyl-2-thienyl)-1H-pyrazole-4-carboxylic acid;
1-(3-Cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[(Cyclohexylacetyl)(1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{(1-Methylethyl) [(4-methylphenyl)carbonyl] amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(4-Bromo-2-chlorophenyl)carbonyl](1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](phenyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{[2-(Dimethylamino)-2-oxoethyl][(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;

3-([(*trans*-4-Methylcyclohexyl)carbonyl]{1-[(methyloxy)carbonyl]-4-piperidinyl}amino)-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{[(*trans*-4-Methylcyclohexyl)carbonyl][1-(methylsulfonyl)-4-piperidinyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methyl-4-piperidinyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{{1-[(Ethylamino)carbonyl]-4-piperidinyl}[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxyllc acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](2-pyrazinylmethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[{[(1S,2R,4S)-2-Hydroxy-4-methylcyclohexyl]carbonyl}(1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{(1-Isopropyl)[(4-methylidenecyclohexyl)carbonyl]amino}-1-phenyl-1*H*-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylmethyl)oxy]phenyl}-1H-pyrazole-4-carboxylic acid;
1-(1H-Indol-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(2-phenylethyl)phenyl]-1H-pyrazole-4-carboxylic acid;
1-(1-Cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[(E)-2-phenylethenyl]-1H-pyrazole-4-carboxylic acid;
1-(4-Methyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
1-Cyclohexyl-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[1-(methylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](phenylmethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{Cyclopentyl[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid;
3-{(1-Acetyl-4-piperidinyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid;
and salts, solvates and esters, and individual enantiomers thereof where appropriate.

Also included in the present invention are pharmaceutically acceptable salt complexes. The present invention also covers the physiologically acceptable salts of the compounds of Formula (I). Suitable physiologically acceptable salts of the compounds of Formula (I) include acid salts, for example sodium, potassium, calcium, magnesium and tetraalkylammonium and the like, or mono- or di- basic salts with the appropriate acid for example organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids and the like.

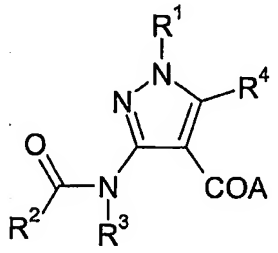
The present invention also relates to solvates of the compounds of Formula (I), for example hydrates.

The present invention also relates to pharmaceutically acceptable esters of the compounds of Formula (I), for example carboxylic acid esters -COOR, in which R is selected from straight or branched chain alkyl, for example n-propyl, n-butyl, alkoxyalkyl (e.g. methoxymethyl), aralkyl (e.g. benzyl), aryloxyalkyl (e.g. phenoxymethyl), aryl (e.g. phenyl optionally substituted by halogen, -C_{1-4}alkyl or -C_{1-4}alkoxy or amino); or for example -$CH_2OC(O)R'$ or -CH_2OCO_2R' in which R' is alkyl (e.g. R' is *t*-butyl). Unless otherwise specified, any alkyl moiety present in such esters preferably contains 1 to 18 carbon atoms, particularly 1 to 4 carbon atoms. Any aryl moiety present in such esters preferably comprises a phenyl group.

It will further be appreciated that certain compounds of the present invention may exist in different tautomeric forms. All tautomers are contemplated to be within the scope of the present invention.

PROCESSES

Compounds of Formula (I) in which A is hydroxy may be prepared from a compound of Formula (II)



(II)

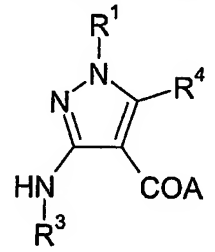
in which A is a protected hydroxy group, for example an alkoxy, benzyloxy or silyloxy group and R^1, R^2, R^3 and R^4 are as defined above for Formula (I). For example when A is methoxy or ethoxy, and R^1, R^2, R^3 and R^4 are as defined above for Formula (I), by treatment with an appropriate base, for example aqueous sodium hydroxide or lithium hydroxide, optionally in a solvent such as methanol, tetrahydrofuran or combinations thereof. Suitably, the

temperature is in the range 25 to 100°C, more preferably 50 to 100°C. Alternatively, when A is methoxy or ethoxy and R^1, R^2, R^3 and R^4 are as defined above for Formula (I), by treatment with lithium iodide in a suitable solvent such as pyridine, lutidine or collidine, suitably in the temperature range 100-170°C.

For example when A is *tert*-butoxy, and R^1, R^2, R^3 and R^4 are as defined above for Formula (I), by treatment with an appropriate acid, for example trifluoroacetic acid. Suitably, the reaction is carried out in a solvent, for example dichloromethane. Suitably, the temperature is in the range 0 to 50°C, more preferably 15 to 30°C.

For example when A is silyloxy, and R^1, R^2, R^3 and R^4 are as defined above for Formula (I), by treatment with a suitable fluoride source for example tetrabutylammonium fluoride. The reaction is carried out in a suitable solvent, for example tetrahydrofuran. Suitably, the temperature is in the range 0 to 50°C, more preferably 15 to 30°C.

Compounds of Formula (I) in which A is hydroxy, or (II) in which A is an alkoxy, benzyloxy or silyloxy group may be prepared by reaction of a compound of Formula (III)



(III)

in which A is hydroxy or an alkoxy, benzyloxy or silyloxy group, and R^1, R^3 and R^4 are as defined above for Formula (I); with a suitable acylating agent, for example R^2-C(O)-Y, wherein Y is a halo atom, for example chloro or bromo, and R^2 is as defined above for Formula (I). The reaction may be carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example pyridine or triethylamine and thereafter removing any protecting group if desired. Where R^2 represents an aliphatic group, a phosphine such as triphenylphosphine may optionally be used. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts 'Protective Groups in Organic Synthesis', 3rd Ed (1999), J Wiley and Sons.

In a further aspect, a compound of Formula (II) may be prepared by appropriate manipulation of another compound of Formula (II). For example, a compound of Formula (II) in which any substituent comprises -C_{2-4}alkenyl may be prepared from a suitable aldehyde or ketone substituent and a phosphorous ylid generated from a phosphonium salt in the presence of a suitable base, such as potassium *tert*-butoxide, in a suitable solvent such as THF. Optionally, the *trans* and *cis* isomers may be separated by standard techniques known in the art

For example, a compound of Formula (II) in which any substituent comprises -C_{2-4}alkyl may be prepared by reduction of an alkenyl substituent, for example using hydrogen, optionally

under pressure, in the presence of a suitable catalyst such as palladium on carbon, in a suitable solvent such as ethanol.

For example, a compound of Formula (II) in which any substituent comprises $-C(O)NR^AR^B$ may be prepared by reacting a suitable acid substituent with an amine (HNR^AR^B) in the presence of a coupling agent such as HATU, in the presence of a suitable base such as triethylamine, in a suitable solvent such as DMF. Alternatively, a compound of Formula (II) in which any substituent comprises $-C(O)NR^AR^B$ may be prepared by reacting a suitable acid chloride substituent with an amine (HNR^AR^B) in the presence of a suitable base such as triethylamine, in a suitable solvent such as dichloromethane.

For example, a compound of Formula (II) in which any substituent comprises $-NR^EC(O)R^D$ may be prepared by reacting a suitable amine substituent with a carboxylic acid (R^DCO_2H) in the presence of a coupling agent such as HATU, in the presence of a suitable base such as triethylamine, in a suitable solvent such as DMF. Alternatively, a compound of Formula (II) in which any substituent comprises $-NR^EC(O)R^D$ may be prepared by reacting a suitable amine substituent with an acid chloride in the presence of a suitable base such as triethylamine in a suitable solvent such as dichloromethane.

For example, a compound of Formula (II) in which any substituent comprises $-NR^ESO_2R^D$ may be prepared by reacting an amine substituent with a suitable sulfonyl chloride in the presence of a suitable base such as triethylamine, in a suitable solvent such as dichloromethane.

For example, a compound of Formula (II) in which any substituent comprises $-SO_2NR^FR^G$ may be prepared by reacting a sulfonyl chloride substituent with a suitable amine (HNR^FR^G) in the presence of a suitable base such as triethylamine, in a suitable solvent such as dichloromethane.

For example, a compound of Formula (II) in which any substituent comprises $-(CH_2)_nSR^A$, wherein n=0, 1, 2, 3 or 4 may be prepared by reacting a thiol $-(CH_2)_nSH$ substituent or a thiolate salt (for example sodium thiomethoxide) substituent with an alkyl halide R^AX wherein X is a halo atom such as bromo, in a suitable solvent such as DMF, in the presence of a suitable base such as triethylamine.

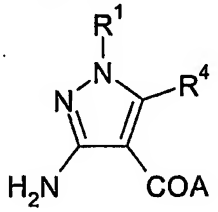
For example, a compound of Formula (II) in which any substituent comprises $-SO_2R^A$ may be prepared by oxidation of a compound in which a substituent represents $-SR^A$, using for example oxone, sodium periodate, 3-chloro perbenzoic acid, or hydrogen peroxide.

For example, a compound of Formula (II) in which any substituent comprises $-(CH_2)_nOR^A$ may be prepared by reacting an alcohol $-(CH_2)_nOH$ substituent, wherein n=0, 1, 2, 3, or 4, with an alkyl halide R^AX wherein X is a halo atom such as bromo in the presence of a suitable base such as triethylamine or sodium hydride, or a compound of Formula (II) in which any substituent comprises $-(CH_2)_pOR^A$ may prepared by reacting an alkyl halide $-(CH_2)_pX$ substituent, where p=1, 2 or 3 and X is a halo atom such as bromo, with an alcohol R^AOH, optionally in the presence of a base such as triethylamine or sodium hydride, or with an alkoxide (for example sodium methoxide) in a suitable solvent such as DMF.

For example, a compound of Formula (II) in which any substituent comprises $-(CH_2)_nNR^AR^B$, where n=0,1, 2, 3, or 4, may be prepared by reacting an amine $-(CH_2)_nNHR^B$ substituent with

an alkyl halide R^AX wherein X is a halo atom such as bromo, in the presence of a suitable base such as triethylamine or sodium hydride, or a compound of Formula (II) in which any substituent comprises $-(CH_2)_nNR^AR^B$ wherein n=0,1, 2, 3, or 4, may be prepared by reacting an aldehyde substituent with an amine, in the presence of a reducing agent such as sodium triacetoxyborohydride, in a suitable solvent such as dichloromethane.

Compounds of Formula (III) in which A is an alkoxy, benzyloxy or silyloxy group may be prepared from compounds of Formula (IV)



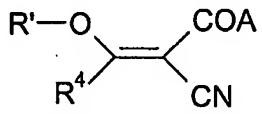
(IV)

in which A is an alkoxy, benzyloxy or silyloxy, and R^1 and R^4 are as defined above for Formula (I), by treatment with a suitable vinyl ether, or a suitable aldehyde or a suitable ketone in the presence of a suitable acid, such as acetic acid, and a suitable reducing agent such as sodium triacetoxyborohydride, in a suitable solvent such as dichloromethane. Alternatively, compounds of Formula (III) in which A is an alkoxy, benzyloxy or silyloxy group may be prepared from compounds of Formula (IV) in which A is an alkoxy, benzyloxy or silyloxy, and R^1 and R^4 are as defined above for Formula (I), by treatment with a suitable alkylating agent R^3-X where X is a halo group such as chloride, bromide or iodide, or X is a sulphonate ester such as methanesulfonate, in suitable solvent such as dimethylformamide in the presence of a suitable base such as triethylamine.

Compounds of Formula (III) in which A is hydroxy may be prepared from compounds of Formula (III) in which A is an alkoxy, benyloxy or silyloxy group, for example by treatment with an appropriate base, acid or fluoride source as described in relation to the preparation of compounds of Formula (I) from compounds of Formula (II).

Compounds of Formula (IV) may be prepared by reaction of compounds of Formula (V)

R^1-$NHNH_2$ (V)



(VI)

in which R^1 is as defined above for Formula (I) with compounds of Formula (VI) in which R^4 and A are as defined above for Formula (II) and R' is $-C_{1-4}$alkyl (such as ethyl) in a suitable solvent such as ethanol or xylene, preferably in the temperature range 50-75°C.

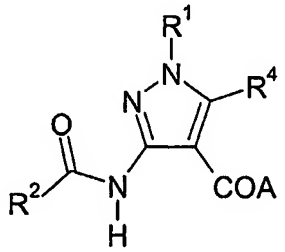
Compounds of Formula (IV) may also be prepared by reaction of compounds of Formula (VII)

R^1-NH-N=P (VII)

in which R^1 is as defined above for Formula (I) and P is a suitable nitrogen protecting group such as benzylidine, with compounds of Formula (VI) in a suitable solvent such as ethanol or xylene, preferably in the temperature range 50-75°C. This is followed by treatment with a suitable acid, such as hydrochloric acid, in a suitable solvent, such as ethanol to effect removal of the protecting group and cyclisation.

Compounds of Formula (V), (VI) and (VII) are commercially available or well known in the art.

Compounds of Formula (II) may also be prepared by reaction of a compound of Formula (VIII)

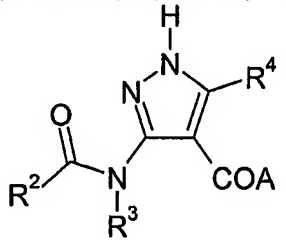


(VIII)

in which A is an alkoxy, benzyloxy or silyloxy group, and R^1, R^2 and R^4 are as defined above for Formula (I); with a suitable alkylating agent R^3-X in which X is a halo atom such as chloro, bromo or iodo, or X is a sulphonate ester such as methanesulfonate, in a suitable solvent such as dimethylformamide, in the presence of a suitable base such as triethylamine and sodium hydride.

Compounds of Formula (VIII) may be prepared from compounds of Formula (IV) by reaction with a suitable acylating agent, for example R^2-C(O)-Y, in which Y is a halo atom, preferably chloro or bromo, and R^2 is as defined above for Formula (I). Suitably, the reaction is carried out in a suitable solvent, for example dichloromethane, in the presence of a suitable base, for example pyridine or triethylamine. For example, where R^2 represents an aliphatic group, a phosphine such as triphenylphosphine may optionally be used in place of an amine base.

Compounds of Formula (II) may also be prepared by reaction of a compound of Formula (IX)

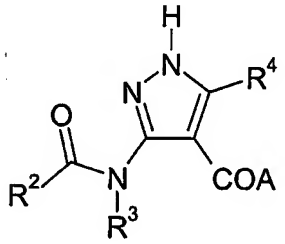


(IX)

in which A is an alkoxy, benzyloxy or silyloxy group, and R^2, R^3 and R^4 are as defined above for Formula (I); by treatment with an aryl, heteroaryl, cycloalkenyl or alkenyl boronic acid in the presence of a copper catalyst such as copper (II) acetate. Suitably, the reaction is carried out in the presence of a base, such as pyridine, in air, and in a suitable solvent such

as dichloromethane or THF, and at a temperature in the range 10-30°C. Alternatively, compounds of Formula (II) in which R^1 represents aryl or heteroaryl may be prepared by reaction of compounds of Formula (IX) with an aryl or heteroaryl halide or triflate in the presence of a copper catalyst such as copper (I) iodide. Suitably, the reaction is carried out in the presence of a base such as potassium carbonate or *trans*-1,2-diaminocyclohexane or a combination thereof in a suitable solvent such as dioxan or pyridine or a combination thereof, and at a temperature in the range 90-110°C.

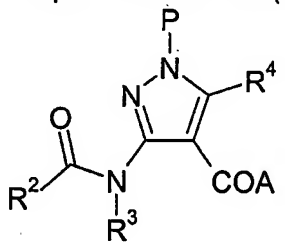
Compounds of Formula (II) in which R^1 represents heteroaryl (for example 2-pyridyl, 2-pyrimidyl, 2-pyrazinyl, 2-pyridazinyl), may also be prepared by reaction of a compound of Formula (IX)



(IX)

in which A is an alkoxy, benzyloxy or silyloxy group, and R^2, R^3 and R^4 are as defined above for Formula (I); by treatment with a 2-halo substituted heteroaryl compound in the presence of a suitable base such as sodium hydride, in a suitable solvent such as dimethylformamide.

Compounds of Formula (IX) in which A is an alkoxy, benzyloxy or silyloxy group may be prepared by deprotection of a compound of Formula (X)



(X)

in which A is an alkoxy, benzyloxy or silyloxy group, and R^2, R^3 and R^4 are as defined above for Formula (I); and P is a suitable protecting group. Suitable protecting groups include, but are not restricted to, benzyl and tert-butyloxycarbonyl . Benzyl groups can be removed by hydrogenation using hydrogen gas with a catalyst such as palladium on carbon in a suitable solvent such as ethanol, optionally in the presence of a suitable acid, for example hydrochloric acid, and optionally conducting the reaction under pressure. *tert*-Butyloxycarbonyl groups may be removed using an acid such as hydrochloric acid or trifluoroacetic acid.

It will be understood by those skilled in the art that compounds of Formula (X) may be prepared from compounds of Formulae (III), (IV) or (VIII) in which the group R^1 is a protecting

group instead of a group as defined for Formula (I), by application of the synthetic routes described above in relation to the synthesis of compounds of Formula (II).

Esters of compounds of Formula (I), in which A is -OR where R is selected from straight or branched chain alkyl, aralkyl, aryloxyalkyl, or aryl, may also be prepared by esterification of a compound of Formula (I) in which A is hydroxy by standard literature procedures for esterification.

It will be appreciated that compounds of Formula (I), (II), (III), (IV), (VIII), (IX) and (X) which exist as diastereoisomers may optionally be separated by techniques well known in the art, for example by column chromatography or recrystallisation. For example, the formation of an ester using a chiral alcohol, separation of the resulting diastereoisomers, and subsequent hydrolysis of the ester to yield the individual enantiomeric acid of Formula (I) (II), (III), (IV), (VIII), (IX) and (X).

It will be appreciated that racemic compounds of Formula (I), (II), (III), (IV), (VIII), (IX) and (X) may be optionally resolved into their individual enantiomers. Such resolutions may conveniently be accomplished by standard methods known in the art. For example, a racemic compound of Formula (I), (II), (III), (IV), (VIII), (IX) and (X) may be resolved by chiral preparative HPLC. Alternatively, racemic compounds of Formula (I), (II), (III), (IV), (VIII), (IX) and (X) which contain an appropriate acidic or basic group, such as a carboxylic acid group or amine group may be resolved by standard diastereoisomeric salt formation with a chiral base or acid reagent respectively as appropriate. Such techniques are well established in the art. For example, a racemic compound may be resolved by treatment with a chiral acid such as (R)-(-)-1,1'-binaphthyl-2,2'-diyl-hydrogen phosphate or (-)-di-O,O'-p-tolyl-L-tartaric acid, in a suitable solvent, for example isopropanol. Alternatively, racemic acid compounds may be resolved using a chiral base, for example (S)-alpha methylbenzylamine, (S)-alpha phenylethylamine, (1S, 2S)-(+)-2-amino-1-phenyl-1,3-propane-diol, (-) ephidrine, quinine, brucine. Individual enantiomers of Formula (II), (III), (IV), (VIII), (IX) and/or (X) may then be progressed to an enantiomeric compound of Formula (I) by the chemistry described above in respect of racemic compounds.

With appropriate manipulation and protection of any chemical functionality, synthesis of compounds of Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section. Suitable protecting groups can be found, but are not restricted to, those found in T W Greene and P G M Wuts 'Protective Groups in Organic Synthesis', 3rd Ed (1999), J Wiley and Sons.

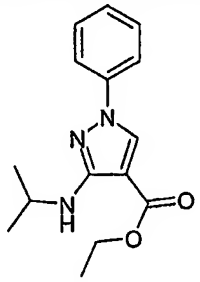
EXAMPLES
ABBREVIATIONS

STRATA cartridge	Dual action SPE cartridge available from Phenomenex
SPE	solid phase extraction column
TFA	trifluoroacetic acid
HPLC	high pressure liquid chromatography
DCM	dichloromethane
DMF	N,N-dimethylformamide
THF	tetrahydrofuran
EtOAc	ethyl acetate
AcOH	acetic acid
DME	1,2-dimethoxyethane
OASIS HLB cartridge	Sample extraction cartridge available from Waters
hrs	hours
HATU	*O*-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphate
TBDMS	*tert*-butyldimethylsilyl
HCl	hydrochloric acid
MDAP HPLC	reverse phase HPLC on a C_{18} column using a two-solvent gradient elution with (A) water containing formic acid (0.1%) and (B) acetonitrile-water (95:5 v/v) containing formic acid (0.05%) as the eluents, and analysis of the fractions by electrospray mass spectroscopy.
ISCO Companion	Automated flash chromatography equipment with fraction analysis by UV absorption available from Presearch.

All mass spectroscopy was performed using electrospray as the method of ionisation.

Intermediate 1

Ethyl 3-[(1-methylethyl)amino]-1-phenyl-1*H*-pyrazole-4-carboxylate



Ethyl 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate hydrogen chloride[1] (5 g) was partitioned between ethyl acetate (100 mL) and a half saturated solution of sodium bicarbonate (100 mL), the organic layer was separated, dried (Na_2SO_4) and concentrated to dryness. The

residue (4.21 g) was dissolved in dichloromethane (100 mL), the solution treated with 2-methoxypropene (6.97 mL, 4 eq), acetic acid (4.17 mL, 4 eq), sodium triacetoxyborohydride (7.72 g, 2 eq) and stirred at room temperature under nitrogen overnight. The reaction mixture was concentrated to dryness, diluted with water (100 mL), adjusted to pH7 with the addition of sodium bicarbonate and extracted with ethyl acetate (2 X 100 mL). The combined extracts were washed with brine, dried (Na_2SO_4), concentrated to dryness and purified by silica gel chromatography, eluting with ethyl acetate/cyclohexane (1: 20) to give the title compound.

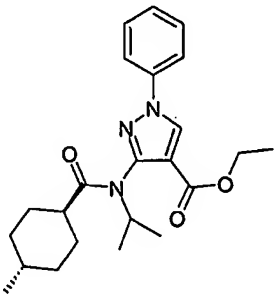
MS calcd for $(C_{15}H_{19}N_3O_2 + H)^+$: 274

MS found (electrospray): $(M+H)^+ = 274$

1. Massa, Silvio; Mai, Antonello; Artico, Marino; Corelli, Federico; *J.Heterocycl.Chem.*; 27; 6; 1990; p1805-1808

Intermediate 2

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-phenyl-1*H*-pyrazole-4-carboxylate



A solution of Intermediate 1 (158 mg) in dichloromethane (2 mL) was treated with *trans*-4-methylcyclohexanecarbonyl chloride[2] (185 mg), triphenyl phosphine (258 mg) and stirred at 45°C overnight. The reaction mixture was diluted with dichloromethane (3 mL), washed with sodium bicarbonate (6 mL), dried (via a hydrophobic frit) and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with ethyl acetate/cyclohexane (0:100, 5:95, 10:90, 15:85 to 100:0) to give the title compound.

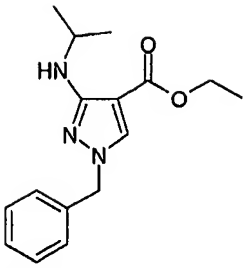
MS calcd for $(C_{23}H_{31}N_3O_3 + H)^+$: 398

MS found (electrospray): $(M+H)^+ = 398$

2. WO 2004/052885

Intermediate 3

Ethyl 3-[(1-methylethyl)amino]-1-(phenylmethyl)-1H-pyrazole-4-carboxylate



Prepared by a similar method to that described for Intermediate 1 from ethyl 3-amino-1-(phenylmethyl)-1H-pyrazole-4-carboxylate[3].

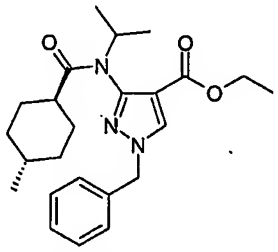
MS calcd for $(C_{16}H_{21}N_3O_2 + H)^+$: 288

MS found (electrospray): $(M+H)^+ = 288$

3. *Chem.Pharm.Bull* 1972, 20(2), 391-398

Intermediate 4

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(phenylmethyl)-1H-pyrazole-4-carboxylate



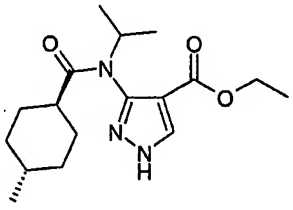
Prepared by a similar method to that described for Intermediate 2 replacing Intermediate 1 with Intermediate 3 to give the title compound.

MS calcd for $(C_{24}H_{33}N_3O_3 + H)^+$: 412

MS found (electrospray): $(M+H)^+ = 412$

Intermediate 5

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

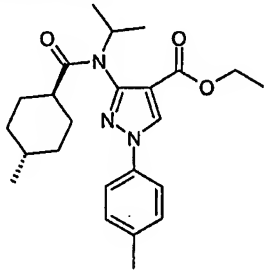


Intermediate 4 (1.52 g, 3.7 mmol) in ethanol (60 mL) and c.hydrochloric acid (0.6 mL) was subjected to atmospheric pressure hydrogenation with 10% palladium on carbon (0.45 g wet) for 16hrs. The reaction was filtered through a Celite pad, and the filter cake washed with ethanol. The combined organics were concentrated to give a gum. This was partitioned between DCM and saturated sodium bicarbonate solution, passed through a hydrophobic frit and the organics concentrated to give the title compound.

MS calcd for $(C_{17}H_{27}N_3O_3 + H)^+$: 322
MS found (electrospray): $(M+H)^+ = 322$

Intermediate 6

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(4-methylphenyl)-1H-pyrazole-4-carboxylate



To p-tolylboronic acid (84 mg, 0.62 mmol) was added copper (II) acetate (85 mg, 0.47 mmol), Intermediate 5 (100 mg, 0.31 mmol) and pyridine (50 uL, 0.62 mmol). The reaction was stirred at room temperature in air for 16 hrs. The solvent removed and the residue purified by MDAP HPLC to give the title compound.
MS calcd for $(C_{24}H_{33}N_3O_3 + H)^+$: 412
MS found (electrospray): $(M+H)^+ = 412$

The following compounds were made from the corresponding commercially available boronic acids by a similar procedure to that described for Intermediate 6:

Intermediate 7

Ethyl 1-(4-hydroxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 8

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylate

Intermediate 9

Ethyl 1-[4-(acetylamino)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 10

Ethyl 1-(4-biphenylyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 11

Ethyl 1-[4-(dimethylamino)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 12
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(methyloxy)phenyl]-1H-pyrazole-4-carboxylate

Intermediate 13
Ethyl 1-(4-acetylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 14
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(trifluoromethyl)oxy]phenyl}-1H-pyrazole-4-carboxylate

Intermediate 15
Ethyl 1-(4-cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 16
Ethyl 1-{4-[(dimethylamino)carbonyl]phenyl}-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 17
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3-thienyl)-1H-pyrazole-4-carboxylate

Intermediate 18
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylate

Intermediate 19
Ethyl 1-(3,5-dimethylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 20
Ethyl 1-(3-chloro-5-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 21
Ethyl 1-[3,5-bis(trifluoromethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 22

Ethyl 1-(1,3-benzodioxol-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 23
Ethyl 1-(2,3-dihydro-1-benzofuran-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 24
Ethyl 1-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 25
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3,4,5-trifluorophenyl)-1H-pyrazole-4-carboxylate

Intermediate 26
Ethyl 1-(4-chlorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 27
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[3-(methyloxy)phenyl]-1H-pyrazole-4-carboxylate

Intermediate 28
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(methylsulfonyl)phenyl]-1H-pyrazole-4-carboxylate

Intermediate 29
Ethyl 1-(2-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 30
Ethyl 1-(3-hydroxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 31
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3-methylphenyl)-1H-pyrazole-4-carboxylate

Intermediate 32
Ethyl 1-(3-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 33
Ethyl 1-(4-aminophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 34
Ethyl 1-(3-chlorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 35
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{3-[(trifluoromethyl)oxy]phenyl}-1H-pyrazole-4-carboxylate

Intermediate 36
Ethyl 1-(4-chloro-3-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 37
Ethyl 1-(4-chloro-3-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 38
Ethyl 1-(3-amino-4-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 39
Ethyl 1-(3-fluoro-4-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 40
Ethyl 1-(3,4-difluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 41
Ethyl 1-[(E)-1-hexen-1-yl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 42
Ethyl 1-[(E)-2-cyclohexylethenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 43

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[(E)-4-methyl-1-penten-1-yl]-1H-pyrazole-4-carboxylate

Intermediate 44

Ethyl 1-[(E)-2-(4-fluorophenyl)ethenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 45

Ethyl 1-(4-ethenylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 46

Ethyl 1-[4-(hydroxymethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 47

Ethyl 1-(4-ethylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 48

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(1-methylethyl)phenyl]-1H-pyrazole-4-carboxylate

Intermediate 49

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylmethyl)oxy]phenyl}-1H-pyrazole-4-carboxylate

Intermediate 50

Ethyl 1-(1H-indol-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 51

Ethyl 1-(4-formylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

This compound was purified by Biotage silica flash column, eluting with ethyl acetate:cyclohexane (20:80) to give the title compound.

Intermediate 52

Ethyl 1-(1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

This compound was purified by partition between DCM and saturated sodium bicarbonate, the organics washed with citric acid solution, passed through a hydrophobic frit and

concentrated. The residue was purified by chromatography on a 10 g silica SPE, eluting with a gradient of ethyl acetate in DCM until the title compound was eluted.

Intermediate 53

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[(E)-2-phenylethenyl]-1H-pyrazole-4-carboxylate

This compound was purified by partition between DCM and saturated sodium bicarbonate, the organics washed with citric acid solution, passed through a hydrophobic frit and concentrated. The residue was purified by chromatography on a 10g silica SPE, eluting with an ethyl acetate in DCM gradient until title compound was isolated.

Intermediate 54

Ethyl 1-(4-phenoxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 55

Ethyl 1-(3-chloro-4-benzyloxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 56

Ethyl 1-(4-*tert*-butyloxycarbonylaminophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 57

Ethyl 1-(4-*tert*-butyloxycarbonylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 58

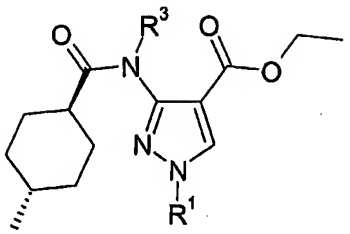
Ethyl 1-((E)-2-*tert*-butyl-ethenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 59

Ethyl 1-(4-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 60

Ethyl 1-(4-(phenylaminocarbonyl)phenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

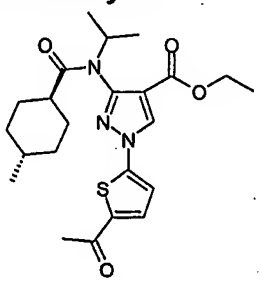


Intermediate Number	Precursor Intermediate Number	Structure		Molecular Formula	Mass Spectrometry	
		R^1	R^3		$(M+H)^+$ Calcd	$(M+H)^+$ Found
7	5	4-OH-Ph	iPr	$C_{23}H_{31}N_3O_4$	414	414
8	5	4-CF_3-Ph	iPr	$C_{24}H_{30}F_3N_3O_3$	466	466
9	5	4-NHAc-Ph	iPr	$C_{25}H_{34}N_4O_4$	455	455
10	5	4-Ph-Ph	iPr	$C_{29}H_{35}N_3O_3$	474	474
11	5	4-NMe_2-Ph	iPr	$C_{25}H_{36}N_4O_3$	441	441
12	5	4-OMe-Ph	iPr	$C_{24}H_{33}N_3O_4$	428	428
13	5	4-Ac-Ph	iPr	$C_{25}H_{33}N_3O_4$	440	440
14	5	4-OCF_3-Ph	iPr	$C_{24}H_{30}F_3N_3O_4$	482	482
15	5	4-CN-Ph	iPr	$C_{24}H_{30}N_4O_3$	423	423
16	5	4-$CONMe_2$-Ph	iPr	$C_{26}H_{36}N_4O_4$	469	469
17	5	3-thienyl	iPr	$C_{21}H_{29}N_3O_3S$	404	404
18	5	3-CF_3-Ph	iPr	$C_{24}H_{30}F_3N_3O_3$	466	466
19	5	3,5-di-Me-Ph	iPr	$C_{25}H_{35}N_3O_3$	426	426
20	5	3-Cl-5-F-Ph	iPr	$C_{23}H_{29}ClFN_3O_3$	450	450
21	5	3,5-di-CF_3-Ph	iPr	$C_{25}H_{29}F_6N_3O_3$	534	534
22	5	3,4-benzodioxol-5-yl	iPr	$C_{24}H_{31}N_3O_5$	442	442
23	5	2,3-dihydro-1-benzofuran-5-yl	iPr	$C_{25}H_{33}N_3O_4$	440	440
24	5	2,3-dihydro-1,4-benzodioxin-6-yl	iPr	$C_{25}H_{33}N_3O_5$	456	456
25	5	3,4,5-tri-F-Ph	iPr	$C_{23}H_{28}F_3N_3O_3$	452	452
26	5	4-Cl-Ph	iPr	$C_{23}H_{30}ClN_3O_3$	432/4	432/4
27	5	3-OMe-Ph	iPr	$C_{24}H_{33}N_3O_4$	428	428
28	5	4-$MeSO_2$-Ph	iPr	$C_{24}H_{33}N_3O_5S$	476	476
29	5	2-F-Ph	iPr	$C_{23}H_{30}FN_3O_3$	412	412
30	5	3-OH-Ph	iPr	$C_{23}H_{31}N_3O_4$	414	414
31	5	3-Me-Ph	iPr	$C_{24}H_{33}N_3O_3$	412	412
32	5	3-F-Ph	iPr	$C_{23}H_{30}FN_3O_3$	416	416
33	5	4-NH_2-Ph	iPr	$C_{23}H_{32}N_4O_3$	413	413
34	5	3-Cl-Ph	iPr	$C_{23}H_{30}ClN_3O_3$	432/4	432/4

35	5	3-OCF_3-Ph	iPr	$C_{24}H_{30}F_3N_3O_4$	482	482
36	5	3-F-4-Cl-Ph	iPr	$C_{23}H_{29}ClFN_3O_3$	450/2	450/2
37	5	3-Me-4-Cl-Ph	iPr	$C_{24}H_{32}ClN_3O_3$	446/8	446/8
38	5	3-NH_2-4-Me-Ph	iPr	$C_{24}H_{34}N_4O_3$	427	427
39	5	3-F-4-Me-Ph	iPr	$C_{24}H_{32}FN_3O_3$	430	430
40	5	3,4-di-F-Ph	iPr	$C_{23}H_{29}F_2N_3O_3$	434	434
41	5	(E)-1-hexen-1-yl	iPr	$C_{23}H_{37}N_3O_3$	404	404
42	5	(E)-2-cyclohexylethenyl	iPr	$C_{25}H_{39}N_3O_3$	430	430
43	5	(E)-4-methyl-1-penten-1-yl	iPr	$C_{23}H_{37}N_3O_3$	404	404
44	5	(E)-2-(4-fluorophenyl)ethenyl	iPr	$C_{25}H_{32}FN_3O_3$	442	442
45	5	4-ethenyl-phenyl	iPr	$C_{25}H_{33}N_3O_3$	424	424
46	5	4-CH_2OH-Ph	iPr	$C_{24}H_{33}N_3O_4$	428	428
47	5	4-Et-Ph	iPr	$C_{25}H_{35}N_3O_3$	426	426
48	5	4-iPr-Ph	iPr	$C_{26}H_{37}N_3O_3$	440	440
49	5	4-BnO-Ph	iPr	$C_{30}H_{37}N_3O_4$	504	504
50	5	5-indolyl	iPr	$C_{25}H_{32}N_4O_3$	437	437
51	5	4-formyl-Ph	iPr	$C_{24}H_{31}N_3O_4$	426	426
52	5	1-cyclohexen-1-yl	iPr	$C_{23}H_{35}N_3O_3$	402	402
53	5	(E)-2-phenylethenyl	iPr	$C_{25}H_{33}N_3O_3$	424	424
54	5	4-PhO-Ph	iPr	$C_{29}H_{35}N_3O_4$	490	490
55	5	3-Chloro-4-BnO-Ph	iPr	$C_{30}H_{36}ClN_3O_4$	539/41	539/41
56	5	4- tBuOCO NH-Ph	iPr	$C_{28}H_{40}N_4O_5$	513	513
57	5	4-tBuOCO-Ph	iPr	$C_{28}H_{39}N_3O_5$	498	498
58	5	(E)-2-tert-butylethenyl	iPr	$C_{25}H_{33}N_3O_3$	376	376
59	5	4-F-Ph	iPr	$C_{23}H_{30}FN_3O_3$	416	416
60	5	4-PhNHCO-Ph	iPr	$C_{30}H_{36}N_4O_3$	517	517

Intermediate 61

Ethyl 1-(5-acetyl-2-thienyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate



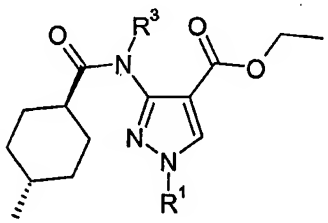
To Intermediate 5 (100 mg, 0.31 mmol) in dry 1,4-dioxane (0.3 mL) was added 2-bromo-5-acetylthiophene (51 mg, 0.25 mmol), potassium carbonate (115 mg, 0.54 mmol), copper (I) iodide (4.9 mg, 0.02 mmol) and *trans*-1,2-diaminocyclohexane (5.8 mg, 0.05 mmol). The reaction was stirred at 110°C overnight, cooled, partitioned between DCM and 2N hydrochloric acid, passed through a hydrophobic frit and the organics concentrated. The crude product was purified by MDAP HPLC to give the title compound.
MS calcd for $(C_{23}H_{31}N_3O_3S + H)^+$: 446
MS found (electrospray): $(M+H)^+ = 446$

The following compounds were made from the corresponding aryl halides by a similar procedure to that described for Intermediate 61:

Intermediate 62
Ethyl 1-(5-chloro-2-thienyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 63
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(5-methyl-2-thienyl)-1H-pyrazole-4-carboxylate

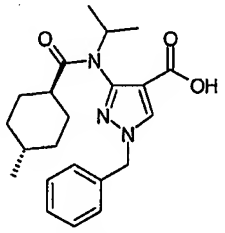
Intermediate 64
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(5-phenyl-2-thienyl)-1H-pyrazole-4-carboxylate



Interme-diate Number	Pre-Cursor Inter-mediate Number	Structure		Molecular Formula	Mass Spectrometry	
		R^1	R^3		$(M+H)^+$ Calcd	$(M+H)^+$ Found
62	5	5-Cl-2-thienyl	iPr	$C_{21}H_{28}ClN_3O_3S$	438	438
63	5	5-Me-2-thienyl	iPr	$C_{22}H_{31}N_3O_3S$	418	418
64	5	5-Ph-2-thienyl	iPr	$C_{27}H_{33}N_3O_3S$	480	480

Intermediate 65

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(phenylmethyl)-1H-pyrazole-4-carboxylic acid



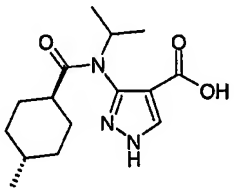
To Intermediate 4 (0.47 g, 1.14 mmol) was added THF (5 ml), ethanol (5 ml) and 2M lithium hydroxide (5 mL). The reaction was stirred at room temperature for 16 hours. The reaction mixture was partitioned between ethyl acetate and 2N hydrochloric acid. The organic layer was separated and washed with brine, dried over sodium sulphate and concentrated to give the title compound.

MS calcd for $(C_{22}H_{29}N_3O_3 + H)^+$: 384

MS found (electrospray): $(M+H)^+ = 384$

Intermediate 66

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

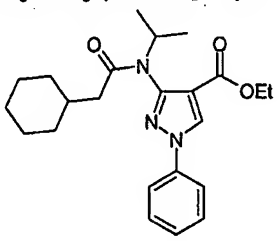


Intermediate 65 (0.44 g, 1.13 mmol) in ethanol (40 mL) and c.hydrochloric acid (0.4 mL) was subjected to atmospheric pressure hydrogenation with 10% palladium on carbon (0.12 g, 30 wt% wet) for 16 hrs. The reaction was filtered through a Celite pad, the pad was washed with ethanol and the filtrate concentrated to give the title compound.

MS calcd for $(C_{15}H_{23}N_3O_3 + H)^+$: 294
MS found (electrospray): $(M+H)^+$ = 294

Intermediate 67

Ethyl 3-[(cyclohexylacetyl)(1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate

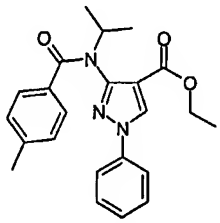


To a mixture of Intermediate 1 (200 mg, 0.86 mmol) in dry DCM (2 mL) was added triphenylphosphine (338 mg, 1.30 mmol) and cyclohexaneacetyl chloride (209 mg, 1.30 mmol). The reaction was stirred overnight at 45°C, then further cyclohexaneacetyl chloride (69 mg, 0.43 mmol) was added and heating continued for 16 hrs. The reaction was cooled, partitioned between DCM and saturated sodium bicarbonate, passed through a hydrophobic frit and organics concentrated. This was purified by 20 g silica SPE cartridge, eluted with 100% cyclohexane then 5% ethyl acetate increments in cyclohexane until the title compound was isolated.

MS calcd for $(C_{23}H_{31}N_3O_3 + H)^+$: 398
MS found (electrospray): $(M+H)^+$ = 398

Intermediate 68

Ethyl 3-{(1-methylethyl)[(4-methylphenyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate

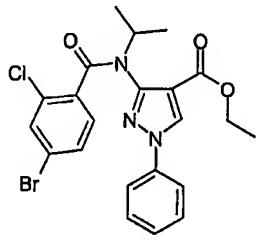


To a mixture of Intermediate 1 (200 mg, 0.86 mmol) in dry pyridine (2 mL) was added 4-methylbenzoyl chloride (201 mg, 1.30 mmol). The reaction was stirred overnight at room temperature, then further 4-methylbenzoyl chloride (67 mg, 0.43 mmol) added and the reaction refluxed overnight. The reaction was cooled, partitioned between DCM and 2N hydrochloric acid, passed through a hydrophobic frit and organics concentrated. This was purified by 10 g silica SPE cartridge, eluted with 100% cyclohexane then 5% ethyl acetate increments in cyclohexane until the title compound was isolated.

MS calcd for $(C_{23}H_{25}N_3O_3 + H)^+$: 392
MS found (electrospray): $(M+H)^+$ = 392

Intermediate 69

Ethyl 3-[[(4-bromo-2-chlorophenyl)carbonyl](1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate



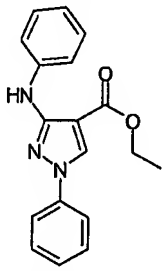
Prepared by a similar method to that described for Intermediate 68 replacing 4-methylbenzoyl chloride with 4-bromo-2-chlorobenzoyl chloride to give the title compound.

MS calcd for $(C_{22}H_{21}BrClN_3O_3 + H)^+$: 490/492

MS found (electrospray): $(M+H)^+$ = 490/492

Intermediate 70

Ethyl 1-phenyl-3-(phenylamino)-1H-pyrazole-4-carboxylate



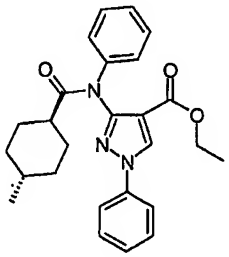
To ethyl 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate (1 g, 4.32 mmol) in dry DCM (50 mL) was added phenyl boronic acid (1.05 g, 8.64 mmol), pyridine (683 mg, 8.64 mmol) and copper (II) acetate (1.18 g, 6.43 mmol). The reaction was stirred at room temperature over 60 hours. The solvent removed and the residue purified by ISCO companion silica chromatography, eluted with a gradient of ethyl acetate in cyclohexane, to give the title compound.

MS calcd for $(C_{18}H_{17}N_3O_2 + H)^+$: 308

MS found (electrospray): $(M+H)^+$ = 308

Intermediate 71

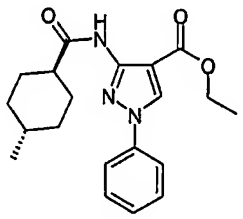
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](phenyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate



Prepared by a similar method to that described for Intermediate 2 replacing Intermediate 1 with Intermediate 70 to give the title compound.
MS calcd for $(C_{26}H_{29}N_3O_3 + H)^+$: 432
MS found (electrospray): $(M+H)^+ = 432$

Intermediate 72

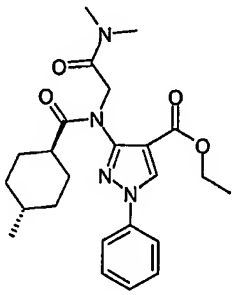
Ethyl 3-{[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate



To ethyl 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate (500 mg, 2.16 mmol) was added dry DCM (10 mL), *trans*-4-methylcyclohexanecarbonyl chloride (0.37 g, 0.24 mmol) and triethylamine (0.45 mL, 0.33 mmol). The reaction was stirred at reflux overnight. The reaction was quenched with saturated sodium bicarbonate, extracted with DCM, organics dried over sodium sulphate and concentrated. Purified by Biotage silica chromatography, eluted with a gradient of ethyl acetate in DCM to give the title compound.
MS calcd for $(C_{20}H_{25}N_3O_3 + H)^+$: 356
MS found (electrospray): $(M+H)^+ = 356$

Intermediate 73

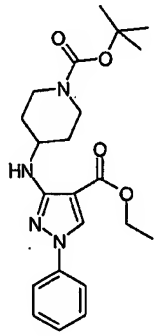
Ethyl 3-{[2-(dimethylamino)-2-oxoethyl][(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate



To Intermediate 72 (200 mg, 0.56 mmol) was added dry DMF (3 mL) then sodium hydride, [60% in oil (20 mg, 0.84 mmol)] and stirred for 30 minutes. N,N-dimethylbromoacetamide (155 mg, 0.94 mmol) added and the reaction stirred at room temperature overnight. The solvent was removed, partitioned between DCM and water, passed through a hydrophobic frit and the organic layer concentrated. Purified by ISCO companion silica chromatography using a gradient of ethyl acetate in cyclohexane to give the title compound.
MS calcd for $(C_{24}H_{32}N_4O_4 + H)^+$: 441
MS found (electrospray): $(M+H)^+ = 441$

Intermediate 74

1,1-Dimethylethyl 4-({4-[(ethyloxy)carbonyl]-1-phenyl-1H-pyrazol-3-yl}amino)-1-piperidinecarboxylate



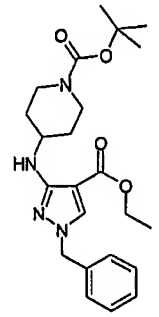
Ethyl 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate (2.5 g, 10.8 mmol) was dissolved in DCM (60 mL), then 1,1-dimethylethyl 4-oxo-1-piperidinecarboxylate (4.3 g, 21.6 mmol), acetic acid (1.9 g, 32.4 mmol) and then sodium triacetoxyborohydride (4.58 g, 21.6 mmol) added. The reaction was stirred at room temperature over 64 hours, partitioned between DCM and saturated sodium bicarbonate, passed through a hydrophobic frit and the organic layer concentrated. Purified by 120 g silica ISCO companion flash column eluting with a gradient of ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_{22}H_{30}N_4O_4 + H)^+$: 415

MS found (electrospray): $(M+H)^+ = 415$

Intermediate 75

1,1-Dimethylethyl 4-({4-[(ethyloxy)carbonyl]-1-phenylmethyl-1H-pyrazol-3-yl}amino)-1-piperidinecarboxylate



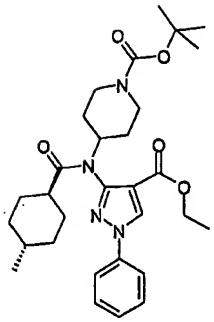
Prepared by a similar method to that described for Intermediate 74 replacing ethyl 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate with ethyl 3-amino-1-(phenylmethyl)-1*H*-pyrazole-4-carboxylate to give the title compound.

MS calcd for $(C_{23}H_{32}N_4O_4 + H)^+$: 429

MS found (electrospray): $(M+H)^+ = 429$

Intermediate 76

1,1-Dimethylethyl 4-{{4-[(ethyloxy)carbonyl]-1-phenyl-1H-pyrazol-3-yl}[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-piperidinecarboxylate



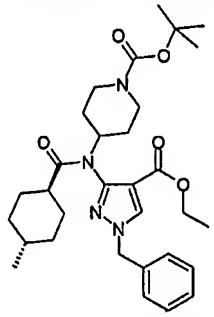
To Intermediate 74 (4.2 g, 0.01 mol) was added dry DCM (70 mL), triethylamine (2.7 mL, 0.02 mol) and *trans*-4-methylcyclohexanecarbonyl chloride (3.2 g, 0.02 mol). The reaction was stirred at 45°C for 7 hours then further *trans*-4-methylcyclohexanecarbonyl chloride (1.6 g, 0.01 mol) added and heated for a further 2 hrs. The reaction was cooled, partitioned between DCM and saturated sodium bicarbonate, passed through a hydrophobic frit and organics concentrated. Purified by ISCO companion silica chromatography using a gradient of ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_{30}H_{42}N_4O_5 + H)^+$: 539

MS found (electrospray): $(M+H)^+ = 539$

Intermediate 77

1,1-Dimethylethyl 4-{{4-[(ethyloxy)carbonyl]-1-phenylmethyl-1H-pyrazol-3-yl}[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-piperidinecarboxylate



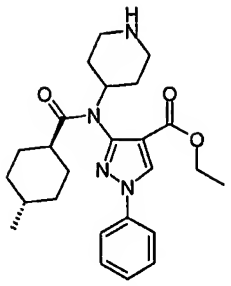
Prepared by a similar method to that described for Intermediate 76 replacing Intermediate 74 with Intermediate 75 to give the title compound.

MS calcd for $(C_{31}H_{44}N_4O_5 + H)^+$: 553

MS found (electrospray): $(M+H)^+ = 553$

Intermediate 78

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](4-piperidinyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate



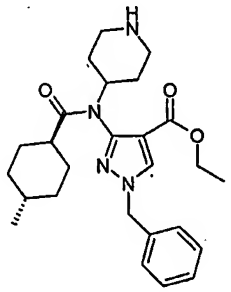
Intermediate 76 (2.7 g, 5.01 mmol) was dissolved in DCM (20 mL) and trifluoroacetic acid (20 mL). The reaction was stirred overnight, solvent removed, partitioned between DCM and saturated sodium bicarbonate and organics concentrated to give the title compound.

MS calcd for $(C_{25}H_{34}N_4O_3 + H)^+$: 439

MS found (electrospray): $(M+H)^+ = 439$

Intermediate 79

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](4-piperidinyl)amino]-1-phenylmethyl-1H-pyrazole-4-carboxylate



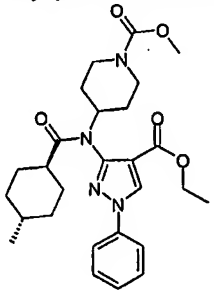
Prepared by a similar method to that described for Intermediate 78 replacing Intermediate 76 with Intermediate 77 to give the title compound.

MS calcd for $(C_{26}H_6N_4O_3 + H)^+$: 453

MS found (electrospray): $(M+H)^+ = 453$

Intermediate 80

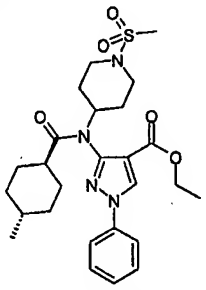
Methyl 4-{{4-[(ethyloxy)carbonyl]-1-phenyl-1H-pyrazol-3-yl}[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-piperidinecarboxylate



To Intermediate 78 (200 mg, 0.46 mmol) was added DCM (2 mL), triethylamine (0.076 mL, 0.55 mmol) and methyl chloroformate (52 mg, 0.52 mmol). The reaction was stirred at room

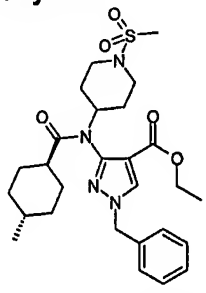
temperature and then partitioned between DCM and 2N hydrochloric acid, passed through a hydrophobic frit and the organic layer concentrated. Purified by ISCO companion silica chromatography with a gradient of ethyl acetate in cyclohexane to give the title compound.
MS calcd for $(C_{27}H_{36}N_4O_5 + H)^+$: 497
MS found (electrospray): $(M+H)^+ = 497$

Intermediate 81
Ethyl 3-{[(*trans*-4-methylcyclohexyl)carbonyl][1-(methylsulfonyl)-4-piperidinyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate



To Intermediate 78 (200 mg, 0.46 mmol) was added DCM (2 mL), triethylamine (0.076 mL, 0.55 mmol) and methanesulfonyl chloride (63 mg, 0.52 mmol). The reaction was stirred at room temperature until complete then partitioned between DCM and 2N hydrochloric acid, passed through a hydrophobic frit and the organic layer concentrated. Purified by ISCO companion silica chromatography with a gradient of ethyl acetate in cyclohexane to give the title compound.
MS calcd for $(C_{26}H_{36}N_4O_5S + H)^+$: 517
MS found (electrospray): $(M+H)^+ = 517$

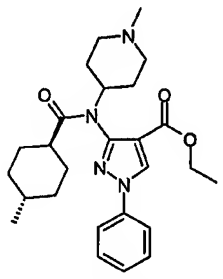
Intermediate 82
Ethyl 3-{[(*trans*-4-methylcyclohexyl)carbonyl][1-(methylsulfonyl)-4-piperidinyl]amino}-1-phenylmethyl-1H-pyrazole-4-carboxylate



Prepared by a similar method to that described for Intermediate 81 replacing Intermediate 78 with Intermediate 79 to give the title compound.
MS calcd for $(C_{27}H_{38}N_4O_5S + H)^+$: 531
MS found (electrospray): $(M+H)^+ = 531$

Intermediate 83

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methyl-4-piperidinyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate



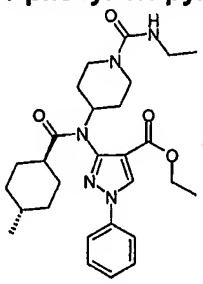
To Intermediate 78 (171 mg, 0.39 mmol) was added methanol (1.2 mL), formic acid (72 mg, 1.56 mmol) and 37% aqueous formaldehyde (0.056 mL, 0.78 mmol). The reaction was heated at 90°C in a reactivial overnight and the solvent removed to give the title compound.

MS calcd for $(C_{26}H_{36}N_4O_3 + H)^+$: 453

MS found (electrospray): $(M+H)^+ = 453$

Intermediate 84

Ethyl 3-{{1-[(ethylamino)carbonyl]-4-piperidinyl}[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate



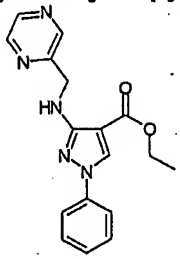
To Intermediate 78 (100 mg, 0.46 mmol) was added DCM (2 mL) and ethyl isocyanate (39 mg, 0.552 mmol). The reaction was stirred at room temperature overnight, partitioned with water, passed through a hydrophobic frit and the organic layer concentrated. Purified by MDAP HPLC to give the title compound.

MS calcd for $(C_{28}H_{39}N_5O_4 + H)^+$: 510

MS found (electrospray): $(M+H)^+ = 510$

Intermediate 85

Ethyl 1-phenyl-3-[(2-pyrazinylmethyl)amino]-1H-pyrazole-4-carboxylate



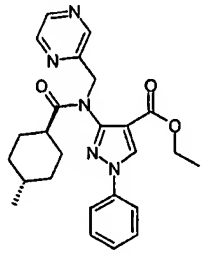
To ethyl 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate (250 mg, 1.08 mmol) was added DCM (6 mL), pyrazine-2-carboxaldehyde (233 mg, 2.16 mmol), acetic acid (0.18 mL, 3.24 mmol) and sodium triacetoxyborohydride (0.46 g, 2.16 mmol). The reaction was stirred overnight at room temperature, partitioned between DCM and water, passed through a hydrophobic frit and the organic layer concentrated. Purified by MDAP HPLC to give the title compound.

MS calcd for $(C_{17}H_{17}N_5O_2 + H)^+$: 324

MS found (electrospray): $(M+H)^+ = 324$

Intermediate 86

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](2-pyrazinylmethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate



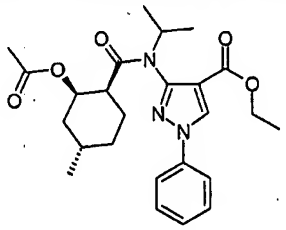
Prepared by a similar method to that described for Intermediate 76 replacing Intermediate 74 with Intermediate 85 to give the title compound.

MS calcd for $(C_{25}H_{29}N_5O_3 + H)^+$: 448

MS found (electrospray): $(M+H)^+ = 448$

Intermediate 87

***Rel*-Ethyl 3-[{[(1S,2R,4S)-2-(acetyloxy)-4-methylcyclohexyl]carbonyl}(1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate**



Racemic

Prepared similarly to the procedure described for Intermediate 2 from Intermediate 1 and *rel*-(1R, 2S, 4R)-2-acetoxy-4-methyl-cyclohexane carboxylic acid chloride[2] to give the title compound.

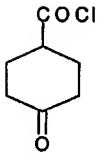
MS calcd for $(C_{25}H_{33}N_3O_5 + H)^+$: 456

MS found (electrospray): $(M+H)^+ = 456$

2. WO2004/052885

Intermediate 88

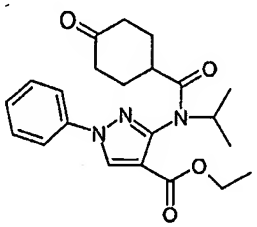
4-Oxocyclohexanecarbonyl chloride



4-Oxocyclohexane carboxylic acid (2.4 g, 16 mmol) was dissolved in DCM (30 mL) and treated with oxalyl chloride (2.95 mL, 33.8 mmol). Diethylformamide (1 drop) was added and the mixture stirred at room temperature for 18 hrs. The reaction mixture was concentrated *in vacuo* to give the title compound as an oil. This was used in the next step without further purification.

Intermediate 89

Ethyl 3-{(1-methylethyl)[(4-oxocyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate



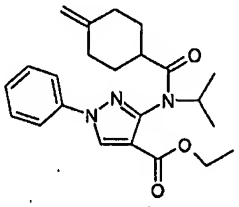
Prepared similarly to the procedure described for Intermediate 2 using Intermediate 1 and Intermediate 88 to give the title compound.

MS calcd for $(C_{22}H_{27}N_3O_4 + H)^+$: 398

MS found (electrospray): $(M+H)^+ = 398$

Intermediate 90

Ethyl 3-{(1-methylethyl)[(4-methylidenecyclohexyl)carbonyl]amino}-1-phenyl-1*H*-pyrazole-4-carboxylate



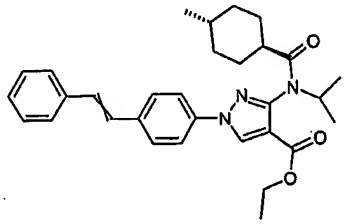
Methyltriphenylphosphonium bromide (540 mg) was dissolved in THF (6 mL) under nitrogen and treated with potassium *tert*-butoxide (1M in THF, 1.35 mL). After 15 minutes a solution of Intermediate 89 (300 mg) in THF (4 mL) was added and the mixture stirred at room temperature for 2 hrs. The reaction was quenched with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated to give a gum. This was purified on a silica column eluting with ethyl acetate : cyclohexane (stepped gradient 10:90 to 20:80) to give the title compound.

MS calcd for $(C_{23}H_{29}N_3O_3 + H)^+$: 396

MS found (electrospray): $(M+H)^+ = 396$

Intermediate 91

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylate



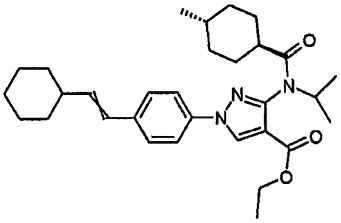
To benzyl triphenylphosphonium bromide (549 mg, 1.4 mmol) was added THF (6 mL) and 1M potassium t-butoxide in THF (1.26 mL, 1.26 mmol). The reaction was stirred for 10 mins then Intermediate 51 (300 mg, 0.7 mmol) in THF (3 mL) added and stirred at room temperature for 2 hrs. Saturated ammonium chloride was added and the mixture extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated. Purified by 20 g silica SPE, loaded in DCM, eluted with ethyl acetate:cyclohexane (1:9) until the title compound was isolated as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{31}H_{37}N_3O_3 + H)^+$: 500

MS found (electrospray): $(M+H)^+ = 500$

Intermediate 92

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-cyclohexylethenyl]phenyl}-1H-pyrazole-4-carboxylate



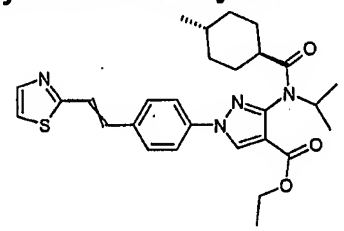
To cyclohexylmethyl triphenylphosphonium chloride (383 mg, 0.96 mmol) in THF (1.5 mL) under nitrogen at 0 °C was added n-BuLi (0.63 mL, 1.6 M solution in hexane) and the mixture stirred for one minute when a solution was obtained. A solution of Intermediate 51 (408 mg, 0.96 mmol) in THF (1.5 mL) was added and the mixture stirred for one hour at 0 C. Saturated ammonium chloride was added and the mixture extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulphate and concentrated. Purified by 50 g silica SPE, eluted with cyclohexane, then a stepwise gradient of ethyl acetate:cyclohexane (1:9, 2:8, 3;7, etc) until the title compound was isolated as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{31}H_{43}N_3O_3 + H)^+$: 506

MS found (electrospray): $(M+H)^+ = 506$

Intermediate 93

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-thiazole-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



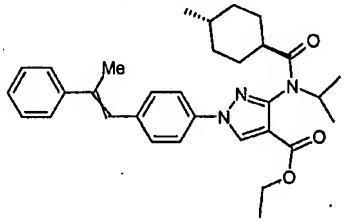
Similarly prepared by the procedure described for Intermediate 91 using 2-thiazolemethyl triphenylphosphonium chloride, and purified using a silica SPE cartridge, eluted with cyclohexane, then a stepwise gradient of ethyl acetate:cyclohexane (1:9, 2:8, 3;7, etc) until the title compound was isolated as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{28}H_{34}N_4O_3S + H)^+$: 507

MS found (electrospray): $(M+H)^+ = 507$

Intermediate 94

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-phenyl-2-methyl-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



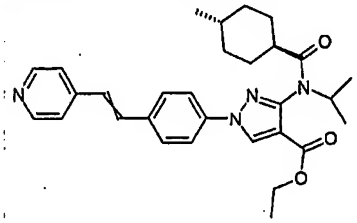
Similarly prepared by the procedure described for Intermediate 91 using diethyl 1-phenethyl phosphonate. Purification was by ISCO Companion silica chromatography, eluted with ethyl acetate:cyclohexane (1:9 then 2:8), to give the title compound as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{32}H_{39}N_3O_3 + H)^+$: 514

MS found (electrospray): $(M+H)^+ = 514$

Intermediate 95

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-(4-pyridyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



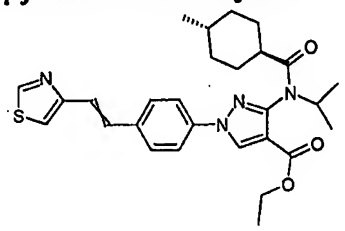
Similarly prepared by the procedure described for Intermediate 91 using 4-pyridylmethyl triphenylphosphonium chloride. Purification was by MDAP HPLC, to give the title compound as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{30}H_{36}N_4O_3 + H)^+$: 501

MS found (electrospray): $(M+H)^+ = 501$

Intermediate 96

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-(4-thiazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



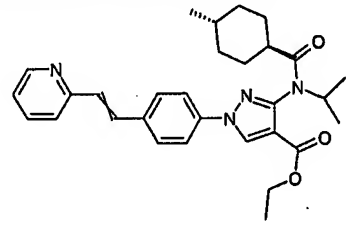
Similarly prepared by the procedure described for Intermediate 91 using 4-thiazolylmethyl triphenylphosphonium chloride. Purification was by SPE silica cartridge, eluted with ethyl acetate:hexane (20:80), to give the title compound as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{28}H_{34}N_4O_3S + H)^+$: 507

MS found (electrospray): $(M+H)^+ = 507$

Intermediate 97

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-(2-pyridyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



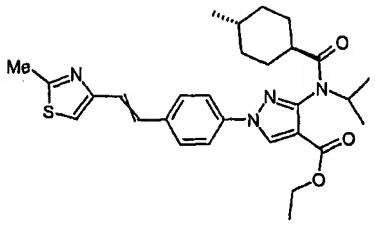
Similarly prepared by the procedure described for Intermediate 91 using 2-pyridylmethyl triphenylphosphonium chloride (hydrochloride salt). Purification was by ISCO Companion silica chromatography, eluted with ethyl acetate:cyclohexane (1:9 then 2:8), to give the title compound as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{30}H_{36}N_4O_3 + H)^+$: 501

MS found (electrospray): $(M+H)^+ = 501$

Intermediate 98

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-(2-methyl-4-thiazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate

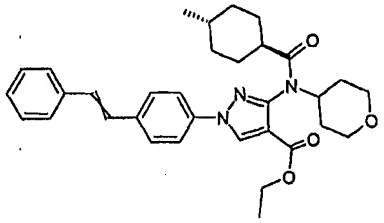


Similarly prepared by the procedure described for Intermediate 91 using 2-methyl-4-thiazolemethyl triphenylphosphonium chloride. Purification was by SPE silica cartridge, eluted with a gradient of ethyl acetate:cyclohexane, to give the title compound as a mixture of *cis* and *trans* isomers (ratio ~ 1:4). Data for the *trans* isomer given.

^{1}H NMR ($CDCl_3$) δ 8.55 (1H, s), 7.71 (2H, d), 4.68 (1H, m), 7.65 (2H, d), 7.48 (1H, d), 7.10 (1H, d), 7.09 (1H, s), 4.95 (1H, m), 4.30 (2H, m), 2.18 (2H, br), 2.80 (3H, s), 1.95 (1H, m), 1.9-0.5 (21H, m).

Intermediate 99

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(E/Z)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylate



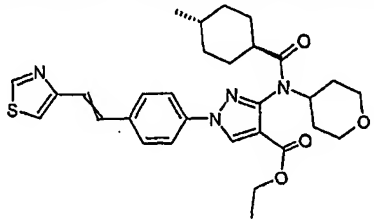
Similarly prepared by the procedure described for Intermediate 91 using benzyl triphenylphosphonium chloride and Intermediate 145. Purification was by ISCO Companion silica chromatography, eluted with a gradient of ethyl acetate:cyclohexane (0% to 50%), to give the title compound as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{33}H_{39}N_3O_4 + H)^+$: 542

MS found (electrospray): $(M+H)^+$ = 542

Intermediate 100

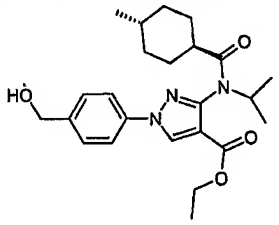
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(E/Z)-2-(4-thiazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



Similarly prepared by the procedure described for Intermediate 91 using 4-thiazolemethyl triphenylphosphonium chloride and Intermediate 145. Purification was by ISCO Companion

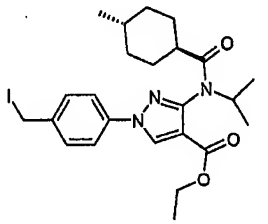
silica chromatography, eluted with a gradient of ethyl acetate:cyclohexane (5% to 50%), to give the title compound as a mixture of *cis* and *trans* isomers.
MS calcd for $(C_{30}H_{36}N_4O_4S + H)^+$: 549
MS found (electrospray): $(M+H)^+ = 549$

Intermediate 101
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-hydroxymethyl-phenyl}-1H-pyrazole-4-carboxylate



To a solution of Intermediate 51 (534 mg, 1.26 mmol) in ethanol (10 mL) was added sodium borohydride (72 mg) and the mixture stirred at room temperature for 30 minutes. The reaction was quenched with dilute aqueous hydrochloric acid and the solvent removed in vacuo. The residue was partitioned between ethyl acetate and dilute HCl (2N), the organic layer washed with water, dried (Na_2SO_4) and concentrated to give the title compound.
MS calcd for $(C_{24}H_{33}N_3O_4 + H)^+$: 428
MS found (electrospray): $(M+H)^+ = 428$

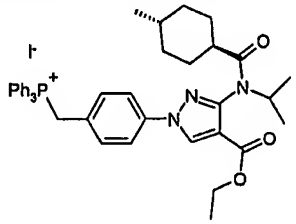
Intermediate 102
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-iodomethyl-phenyl}-1H-pyrazole-4-carboxylate



To a solution of Intermediate 101 (515 mg, 1.2 mmol) in THF (10 mL) was added triphenyl phosphine (316 mg, 1.2 mmol) and imidazole (106 mg, 1.56 mmol), followed by iodine (305 mg, 1.2 mmol) and the mixture stirred at room temperature for 2 hours. The reaction was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. This was purified by SPE (silica) eluted with ethyl acetate:cyclohexane (15:85) to give the title compound.
MS calcd for $(C_{24}H_{32}IN_3O_3 + H)^+$: 538
MS found (electrospray): $(M+H)^+ = 538$

Intermediate 103

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-triphenylphosphoniummethyl-phenyl}-1H-pyrazole-4-carboxylate



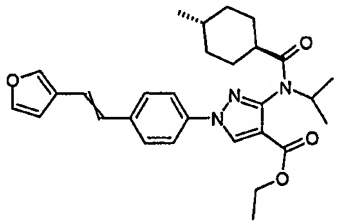
To a solution of Intermediate 102 (230 mg, 0.43 mmol) in THF (3 mL) was added triphenyl phosphine (146 mg, 0.57 mmol) and the mixture heated at 100 °C for 18 hours. The solvent was removed in vacuo to give the title compound.

MS calcd for ylid $(C_{42}H_{46}N_3O_3P + H)^+$: 672

MS found (electrospray): $(M+H)^+ = 672$

Intermediate 104

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(E/Z)-2-(3-furanyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



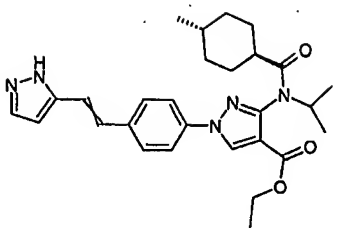
To a solution of Intermediate 103 (200 mg, 0.25 mmol) in THF (2 mL) was added a solution of potassium *tert*-butoxide in THF (1M, 0.25 mL). After stirring for 3 minutes under nitrogen, a solution of furan-3-carboxaldehyde (36 mg, 0.37 mmol) was added and the mixture stirred at room temperature for 2 hours. Saturated ammonium chloride solution was added and the mixture extracted with ethyl acetate. The organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. This was purified by chromatography (silica) eluted with ethyl acetate:cyclohexane (20:80) to give the title compound as a mixture of *cis* and *trans* isomers.

MS calcd for $(C_{29}H_{35}N_3O_3 + H)^+$: 490

MS found (electrospray): $(M+H)^+ = 490$

Intermediate 105

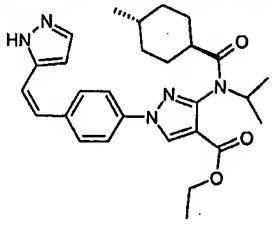
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(E/Z)-2-(3-pyrazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



Similarly prepared by the procedure described for Intermediate 104 using 3-pyrazole carboxaldehyde and Intermediate 103. Purification was by ISCO Companion silica chromatography, eluted with a gradient of ethyl acetate:cyclohexane (12% to 75%), to give the title compound as the pure cis isomer and a mixture of *cis* and *trans* isomers.
cis and *trans* isomers
MS calcd for $(C_{28}H_{35}N_5O_3 + H)^+$: 490
MS found (electrospray): $(M+H)^+ = 490$

Intermediate 106

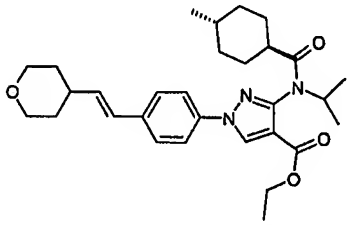
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(Z)-2-(3-pyrazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate



Cis isomer from Intermediate 105.
MS calcd for $(C_{28}H_{35}N_5O_3 + H)^+$: 490
MS found (electrospray): $(M+H)^+ = 490$

Intermediate 107

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(E)-2-(tetrahydro-2H-pyran-4-yl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylate

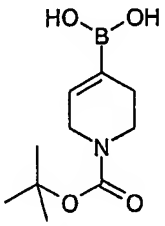


Similarly prepared by the procedure described for Intermediate 104 using 4-(tetrahydro-2H-pyran)carboxaldehyde. Purification was by ISCO Companion silica chromatography, eluted with ethyl acetate:cyclohexane (15:85), to give the title compound as the *trans* isomer.
MS calcd for $(C_{30}H_{41}N_3O_4 + H)^+$: 508

MS found (electrospray): $(M+H)^+ = 508$

Intermediate 108

(1-{[(1,1-Dimethylethyl)oxy]carbonyl}-1,2,3,6-tetrahydro-4-pyridinyl)boronic acid



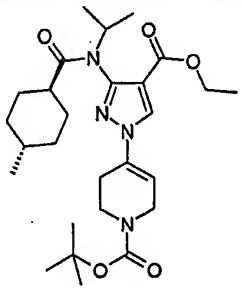
Sodium periodate (2.08 g, 9.75 mmol) was added in portions to a mixture of 1,1-dimethylethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2H)-pyridine-carboxylate (1.0 g, 3.25 mmol, TDC Research Inc) and ammonium acetate (750 mg, 9.74 mmol) in acetone (40 mL) and water (40 mL) at room temperature, under nitrogen. The reaction was stirred overnight, filtered through a Celite pad, washed with acetone and the organic solvent removed. Brine (50 mL) was added and the solution was extracted three times with ethyl acetate. The combined organic layers were dried over sodium sulphate and concentrated to give the title compound.

MS calcd for $(C_{10}H_{18}NO_4 + H)^+$: 228

MS found (electrospray): $(M+H)^+ = 228$

Intermediate 109

1,1-Dimethylethyl 4-{4-[(ethyloxy)carbonyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazol-1-yl}-3,6-dihydro-1(2H)-pyridinecarboxylate



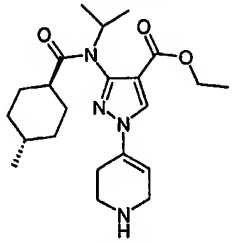
Copper (II) acetate (210 mg, 1.17 mmol) was added to a DCM (10 mL) solution of Intermediate 5 (250 mg, 0.778 mmol) and Intermediate 108 (353 mg, 1.56 mmol). The reaction was stirred at room temperature, in air for 24 hrs, filtered through Celite, partitioned between DCM and saturated sodium bicarbonate, passed through a hydrophobic frit and the organic layer concentrated. Purified by 20 g silica SPE eluted DCM in cyclohexane (0-100%) then ethyl acetate:cyclohexane (1:4) to give the title compound.

MS calcd for $(C_{27}H_{42}N_4O_5 + H)^+$: 503

MS found (electrospray): $(M+H)^+ = 503$

Intermediate 110

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-pyrazole-4-carboxylate



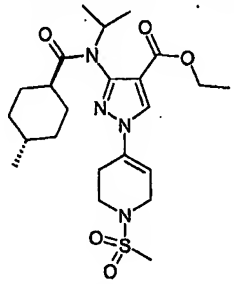
Hydrogen chloride in 1,4-dioxane (4 mL, 4N) was added to a solution of Intermediate 109 (330 mg, 0.66 mmol) in 1,4-dioxane, then stirred at room temperature, under nitrogen for 2 hrs. The solvent was removed and the residue co-evaporated with diethyl ether. The residue was dissolved in methanol (5 mL) and loaded onto a 10 g SCX-2 SPE cartridge. The column was washed with methanol (3 column volumes) then eluted with 10% 0.88 ammonia in methanol to give the title compound.

MS calcd for $(C_{22}H_{34}N_4O_3 + H)^+$: 403

MS found (electrospray): $(M+H)^+ = 403$

Intermediate 111

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[1-(methylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-1H-pyrazole-4-carboxylate



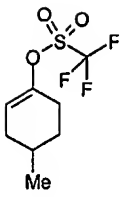
Triethylamine (0.028 mL, 0.2 mmol) followed by methanesulfonyl chloride (0.015 mL, 0.2 mmol) was added to a DCM (3 mL) solution of Intermediate 110 (68.5 mg, 0.17 mmol). The reaction was stirred for 1 hour at room temperature, under nitrogen, then loaded onto a 2 g STRATA cartridge and eluted with DCM (3 column volumes) then methanol (3 column volumes) until the title compound was isolated.

MS calcd for $(C_{23}H_{36}N_4O_5S + H)^+$: 481

MS found (electrospray): $(M+H)^+ = 481$

Intermediate 112

4-Methyl-1-cyclohexen-1-yl trifluoromethanesulfonate

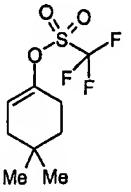


Triflic anhydride (1.57 mL, 9.37 mmol) was added dropwise to a solution of 4-methylcyclohexanone (1 g, 8.92 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (2 g, 9.8 mmol) in dry DCM (50 mL). The reaction was stirred at room temperature, under nitrogen overnight. The solution was filtered and concentrated to 10 mL, applied to a 20 g silica SPE and eluted with DCM to give the title compound.

Thin layer chromatography (silica) 1:9 ethyl acetate:cyclohexane R_f = 0.9 (UV detection).

Intermediate 113

4,4-Dimethyl-1-cyclohexen-1-yl trifluoromethanesulfonate



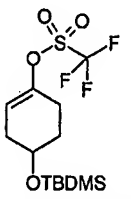
Prepared by a similar method to that described for Intermediate 112 using 4,4-dimethylcyclohexanone[4], to give the title compound.

Thin layer chromatography (silica) 1:9 ethyl acetate:cyclohexane R_f = 0.9 (detection with $KMnO_4$).

4. Tetrahedron (1994), 50 (4) 973-978.

Intermediate 114

4-*tert*-Butyldimethylsilyloxy-1-cyclohexen-1-yl trifluoromethanesulfonate

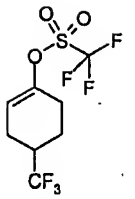


Prepared by a similar method to that described for Intermediate 112 using 4-*tert* butyldimethylsilylcyclohexanone, to give the title compound.

Thin layer chromatography (silica) 1:9 ethyl acetate:cyclohexane R_f = 0.95 (detection with $KMnO_4$).

Intermediate 115

4-Trifluoromethyl-1-cyclohexen-1-yl trifluoromethanesulfonate

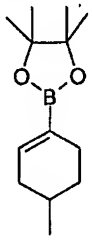


Prepared by a similar method to that described for Intermediate 112 using 4-trifluoromethylcyclohexanone, to give the title compound.

^{1}H NMR ($CDCl_3$): δ 5.79 (1H, d), 2.57-2.12 (6H, m), 1.78 (1H, m).

Intermediate 116

4,4,5,5-Tetramethyl-2-(4-methyl-1-cyclohexen-1-yl)-1,3,2-dioxaborolane

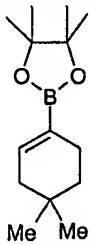


[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium (II) (167 mg, 0.20 mmol) was added to a solution of Intermediate 112 (1 g, 4.09 mmol) and bis(pinacolato)diboron (3.11 g, 12.27 mmol) and potassium acetate (1.8 g, 18.4 mmol) in dry DMF (5 mL). The reaction was stirred at 80°C, under nitrogen, for 24 hours. The reaction was cooled, solvent removed, partitioned between diethyl ether and water, organics washed twice further with water, dried over sodium sulphate and concentrated. Purified by 50 g silica SPE, loaded in DCM, eluted with a gradient of DCM in cyclohexane to give the title compound which was used without further purification.

Thin layer chromatography (silica) 1:9 ethyl acetate:cyclohexane R_f = 0.8

Intermediate 117

4,4,5,5-Tetramethyl-2-(4,4-dimethyl-1-cyclohexen-1-yl)-1,3,2-dioxaborolane

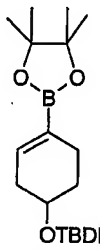


Prepared by a similar method to that described for Intermediate 116 using Intermediate 113, to give the title compound.

Thin layer chromatography (silica) cyclohexane R_f = 0.2 (uv detection).

Intermediate 118

(1,1-Dimethylethyl)(dimethyl){[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-cyclohexen-1-yl]oxy}silane

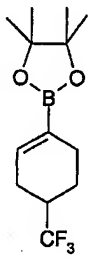


Prepared by a similar method to that described for Intermediate 116 using Intermediate 114, to give the title compound.

Thin layer chromatography (silica) 5:95 ethyl acetate:cyclohexane R_f = 0.9 (uv detection).

Intermediate 119

4,4,5,5-Tetramethyl-2-[4-(trifluoromethyl)-1-cyclohexen-1-yl]-1,3,2-dioxaborolane

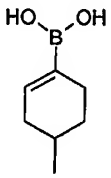


Prepared by a similar method to that described for Intermediate 116 using Intermediate 115, to give the title compound.

^{1}H NMR ($CDCl_3$): δ 6.53 (1H, d), 2.4-1.97 (5H, m), 1.45 (1H, m), 1.27 (12H, s), 1.22 (1H, m).

Intermediate 120

(4-Methyl-1-cyclohexen-1-yl)boronic acid



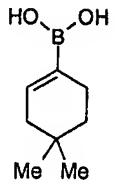
Prepared by a similar method to that described for Intermediate 108 replacing 1,1-dimethylethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2H)-pyridinecarboxylate with Intermediate 116 to give the crude title compound used without further purification.

MS calcd for $(C_7H_{13}BO_2 + H)^+$: 141

MS found (electrospray): $(M+H)^+$ = 141

Intermediate 121

(4,4-Dimethyl-1-cyclohexen-1-yl)boronic acid

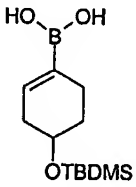


Prepared by a similar method to that described for Intermediate 108 using Intermediate 117, to give the title compound, used directly in the next step.

^{1}H NMR ($CDCl_3$): δ 6.9 for characteristic alkene proton.

Intermediate 122

(4-{[(1,1-dimethylethyl)(dimethyl)silyl]oxy}-1-cyclohexen-1-yl)boronic acid



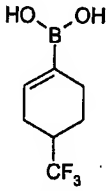
Prepared by a similar method to that described for Intermediate 108 using Intermediate 118, to give the title compound, used directly in the next step.

^{1}H NMR ($CDCl_3$): δ 6.8 for characteristic alkene proton.

Thin layer chromatography (silica) 5:95 ethyl acetate:cyclohexane R_f = 0.8 (uv detection).

Intermediate 123

[4-(Trifluoromethyl)-1-cyclohexen-1-yl]boronic acid

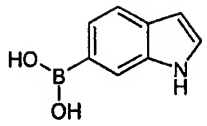


Prepared by a similar method to that described for Intermediate 108 using Intermediate 119, to give the title compound, used directly in the next step.

^{1}H NMR ($CDCl_3$): δ 7.28 (1H, d), 2.52-1.98 (7H, m), 1.5 (2H, m).

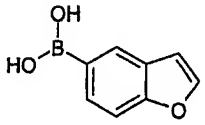
Intermediate 124

6-Indoleboronic acid



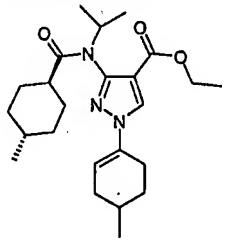
Prepared by a similar method to that described for Intermediate 108 using 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole to give the title compound.
MS calcd for $(C_8H_8BNO_2 - H)^-$: 161
MS found (electrospray): $(M-H)^-$ = 161

Intermediate 125
5-Benzofuranboronic acid



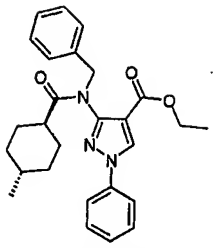
Prepared by a similar method to that described for Intermediate 108 using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-benzofuran to give the title compound.
MS calcd for $(C_8H_7BO_3 + H)^+$: 163
MS found (electrospray): $(M+H)^+$ = 163

Intermediate 126
Ethyl 1-(4-methyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate



Prepared by a similar method to that described for Intermediate 52 using Intermediate 120 to give the title compound.
MS calcd for $(C_{24}H_{37}N_3O_3 + H)^+$: 416
MS found (electrospray): $(M+H)^+$ = 416

Intermediate 127
Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](phenylmethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylate



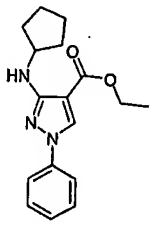
Prepared by a similar method to that described for Intermediate 73, replacing N,N-dimethylbromoacetamide with benzyl bromide and purified by MDAP HPLC to give the title compound.

MS calcd for $(C_{27}H_{31}N_3O_3 + H)^+$: 446

MS found (electrospray): $(M+H)^+ = 446$

Intermediate 128

Ethyl 3-(cyclopentylamino)-1-phenyl-1H-pyrazole-4-carboxylate

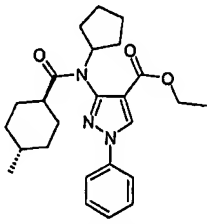


Prepared by a similar method to that described for Intermediate 85, replacing pyrazine-2-carboxaldehyde with cyclopentanone and purified by ISCO Companion silica chromatography (12 g cartridge), eluted with 0-80% ethyl acetate in cyclohexane to give the title compound.

^{1}H NMR ($CDCl_3$): δ 8.39 (1H, s), 7.61 (2H, d), 7.43 (2H, t), 7.22 (1H, t), 5.41 (1H, br), 4.30 (2H, m), 4.14 (1H, m), 2.11 (2H, m), 1.78-1.70 (2H, br), 1.69-1.53 (4H, br), 1.36 (3H, t)

Intermediate 129

Ethyl 3-{cyclopentyl[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate

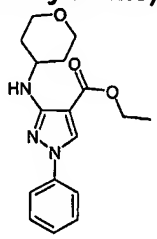


Prepared by a similar method to that described for Intermediate 76, replacing Intermediate 74 with Intermediate 128 and purified by silica Biotage flash column, eluted with 5% acetonitrile in DCM to give the title compound.

^{1}H NMR ($CDCl_3$): δ 8.50 (1H, s), 7.72 (2H, d), 7.53 (2H, t), 7.41 (1H, t), 4.86 (1H, m), 4.30 (2H, m), 2.16-1.75 (5H, br), 1.73-1.43 (7H, br), 1.40-1.25 (5H, br), 1.18 (1H, m), 0.75 (3H, d), 0.70-0.53 (2H, br)

Intermediate 130

Ethyl 1-phenyl-3-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazole-4-carboxylate

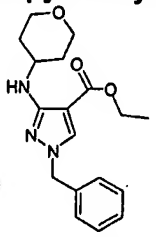


Prepared by a similar method to that described for Intermediate 85, replacing pyrazine-2-carboxaldehyde with tetrahydro-4H-pyran-4-one and purified by ISCO Companion silica chromatography (12 g cartridge), eluted with 0-80% ethyl acetate in cyclohexane to give the title compound.

^{1}H NMR ($CDCl_3$): δ 8.15 (1H, s), 7.64 (2H, d), 7.44 (2H, t), 7.28 (1H, hidden under solvent peak), 5.46 (1H, d), 4.30 (2H, q), 4.02 (2H, d), 3.88 (1H, m), 3.55 (2H, t), 2.15 (2H, d), 1.62 (2H, m), 1.36 (3H, t).

Intermediate 131

Ethyl 1-phenylmethyl-3-(tetrahydro-2H-pyran-4-ylamino)-1H-pyrazole-4-carboxylate



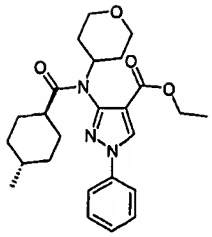
Prepared by a similar method to that described for Intermediate 85, replacing pyrazine-2-carboxaldehyde with tetrahydro-4H-pyran-4-one and ethyl 3-amino-1-phenyl-1*H*-pyrazole-4-carboxylate with ethyl 3-amino-1-phenylmethyl-1*H*-pyrazole-4-carboxylate.[3] Purification was by ISCO Companion silica chromatography (330 g cartridge), eluted with 5-60% ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_{18}H_{23}N_3O_3 + H)^+$: 330

MS found (electrospray): $(M+H)^+$ = 330

Intermediate 132

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-phenyl-1H-pyrazole-4-carboxylate

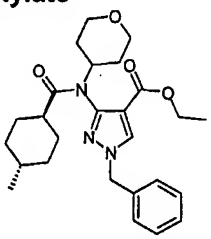


Prepared by a similar method to that described for Intermediate 76, replacing Intermediate 74 with Intermediate 130 and purified by ISCO companion silica flash column, eluted with 0-70% ethyl acetate in cyclohexane to give the title compound.

^{1}H NMR ($CDCl_3$): δ 8.51 (1H, s), 7.71 (2H, d), 7.53 (2H, t), 7.41 (1H, t), 4.83 (1H, m), 4.03 (2H, m), 3.93 (2H, br), 3.50 (2H, q), 2.05 (1H, s), 2.0-1.55 (8H, br), 1.50-1.25 (6H, br), 0.78 (3H, d), 0.76-0.60 (2H, br).

Intermediate 133

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-phenylmethyl-1H-pyrazole-4-carboxylate



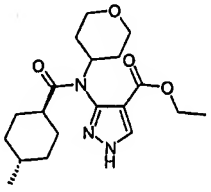
Prepared by a similar method to that described for Intermediate 2, replacing Intermediate 1 with Intermediate 131 and purified by ISCO companion silica flash column, eluted with 10% ethyl acetate in cyclohexane, then a gradient of 10-50% ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_{26}H_{35}N_3O_4 + H)^+$: 454

MS found (electrospray): $(M+H)^+ = 454$

Intermediate 134

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate

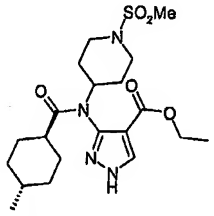


A solution of Intermediate 133 (5.1 g, 11.3 mmol) in ethanol (200 mL) and concentrated hydrochloric acid (2 mL) was subjected to atmospheric hydrogenation using 10% palladium on carbon catalyst (1.35 g) for 16 hours. The mixture was filtered through a Celite pad, the pad washed with ethanol and the combined organics evaporated. The residue was

partitioned between DCM and saturated sodium bicarbonate solution, passed through a hydrophobic frit and the organic layer evaporated to give the title compound.
MS calcd for $(C_{19}H_{29}N_3O_4 + H)^+$: 364
MS found (electrospray): $(M+H)^+ = 364$.

Intermediate 135

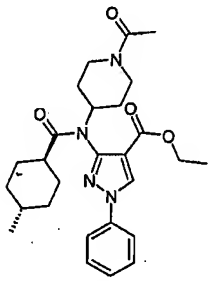
Ethyl 3-{[(*trans*-4-methylcyclohexyl)carbonyl][1-(methylsulfonyl)-4-piperidinyl]amino}-1*H*-pyrazole-4-carboxylate



Prepared by a similar method to that described for Intermediate 134, replacing Intermediate 133 with Intermediate 82 to give the title compound.
MS calcd for $(C_{20}H_{32}N_4O_5S + H)^+$: 441
MS found (electrospray): $(M+H)^+ = 441$

Intermediate 136

Ethyl 3-{(1-acetyl-4-piperidinyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylate



To Intermediate 78 (50 mg, 0.114 mmol) was added DCM (3 mL), acetyl chloride (0.016 mL, 0.23 mmol) and triethylamine (0.23 mmol). The reaction was stirred overnight at room temperature, partitioned between DCM and saturated sodium bicarbonate, the aqueous layer separated and the organic layer concentrated to give the title compound.
MS calcd for $(C_{27}H_{36}N_4O_4 + H)^+$: 481
MS found (electrospray): $(M+H)^+ = 481$

The following compounds were prepared by coupling the appropriate boronic acid derivative to pyrazoles using a similar method to that described for Intermediate 6.

Intermediate 137
Ethyl 1-(4-(6-indolyl)phenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 138
Ethyl 1-(4-(5-benzofuranyl)phenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 139
Ethyl 1-(4-(trifluoromethyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 140
Ethyl 1-(4-(*tert*-butyldimethylsilyloxy)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylate

Intermediate 141
Ethyl 1-(4,4-dimethyl)cyclohexen-1-yl)-3-{[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino}-1H-pyrazole-4-carboxylate

Intermediate 142
Ethyl 1-((4,4-dimethyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate
This compound was purified by ISCO Companion silica chromatography (12 g cartridge), eluted with 0-95% ethyl acetate in cyclohexane to give the title compound.

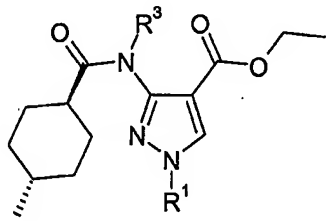
Intermediate 143
Ethyl 1-(cyclohepten-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate

Intermediate 144
Ethyl 1-((4-methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate
This compound was purified by ISCO Companion silica chromatography (12 g cartridge), eluted with 0-50% ethyl acetate in cyclohexane to give the title compound.

Intermediate 145
Ethyl 1-((4-formyl)phenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate

Intermediate 146

Ethyl 1-((4-methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-(methylsulfonyl)-4-piperidinyl]amino]-1H-pyrazole-4-carboxylate

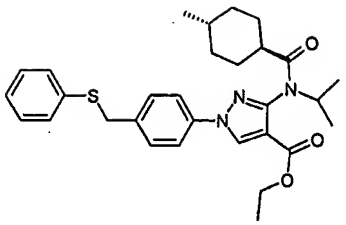


Intermediate Number	Pre-Cursor Intermediate Numbers	Structure		Molecular Formula	Mass Spectrometry	
		R^1	R^3		$(M+H)^+$ Calcd	$(M+H)^+$ Found
137	5, 124	6-indolyl	iPr	$C_{25}H_{32}N_4O_3$	437	437
138	5, 125	5-benzofuranyl	iPr	$C_{25}H_{31}N_3O_4$	438	438
139	5, 123	4-(Trifluoromethyl)-1-cyclohexen-1-yl	iPr	$C_{24}H_{34}F_3N_3O_3$	470	470
140	5, 122	4-(TBDMSO)-1-cyclohexen-1-yl	iPr	$C_{29}H_{49}N_3O_4Si$	532	532
141	5, 121	4,4-(Dimethyl)-1-cyclohexen-1-yl	iPr	$C_{29}H_{39}N_3O_3$	430	430
142	134, 121	4,4-(Dimethyl)-1-cyclohexen-1-yl	pyran-4-yl	$C_{27}H_{41}N_3O_4$	472	472
143	134	1-Cyclohepten-1-yl	pyran-4-yl	$C_{28}H_{39}N_3O_4$	458	458
144	120, 134	4-Methyl-1-cyclohexen-1-yl	pyran-4-yl	$C_{28}H_{39}N_3O_4$	458	458
145	134	4-Formyl Ph	pyran-4-yl	$C_{26}H_{33}N_3O_5$	468	468
146	120, 135	4-Methyl-1-cyclohexen-1-yl	1-Methylsulfonyl-4-piperidinyl	$C_{27}H_{42}N_4O_5S$	535	535

Cyclohepten-1-yl boronic acid and 4-formylphenyl boronic acid are commercially available.

Intermediate 147

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylthio)methyl]phenyl}-1*H*-pyrazole-4-carboxylate



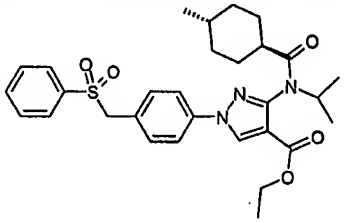
To a solution of Intermediate 102 (137 mg, 0.26 mmol) in ethanol (2 mL) was added sodium thiophenolate (67 mg, 0.51 mmol) and the mixture stirred at room temperature for 2 hours. The ethanol was removed *in vacuo,* the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution, the organic extract dried (Na_2SO_4) and concentrated. This was purified by silica column chromatography, eluted with ethyl acetate:cyclohexane (10:90) to give the title compound.

MS calcd for $(C_{30}H_{37}N_3O_3S + H)^+$: 520

MS found (electrospray): $(M+H)^+ = 520$

Intermediate 148

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylsulfonyl)methyl]phenyl}-1*H*-pyrazole-4-carboxylate



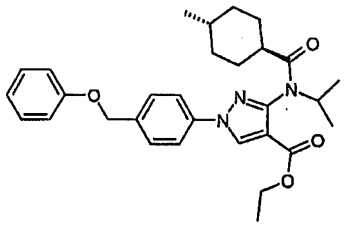
To a solution of Intermediate 147 (119 mg, 0.23 mmol) in ethanol (10 mL) was added a solution of oxone (423 mg, 0.69 mmol) in water (5 mL) and the mixture stirred at room temperature for 18 hours. The solvents were removed *in vacuo,* the residue partitioned between DCM and water, the organic extract passed through a hydrophobic frit and concentrated. This was purified by silica column chromatography, eluted with ethyl acetate:cyclohexane (10:90, then 20:80, then 30:70, and finally 40:60) to give the title compound.

MS calcd for $(C_{30}H_{37}N_3O_5S + H)^+$: 552

MS found (electrospray): $(M+H)^+ = 552$

Intermediate 149

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenyloxy)methyl]phenyl}-1*H*-pyrazole-4-carboxylate



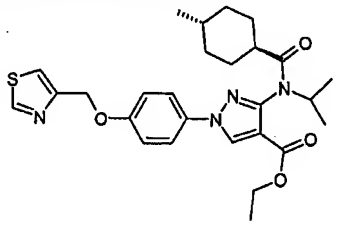
To a solution of Intermediate 102 (137 mg, 0.26 mmol) in acetone (5 mL) was added potassium carbonate (90 mg) and phenol (50 mg) and the mixture stirred at room temperature for 2 days. The solvent was removed *in vacuo,* the residue partitioned between DCM and water, the organic extract passed through a hydrophobic frit and concentrated. This was purified by SPE (silica), eluted with a gradient of ethyl acetate:cyclohexane (20-50%) to give the title compound.

MS calcd for $(C_{30}H_{37}N_3O_4 + H)^+$: 504

MS found (electrospray): $(M+H)^+ = 504$

Intermediate 150

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(1,3-thiazol-4-ylmethyl)oxy]phenyl}-1*H*-pyrazole-4-carboxylate



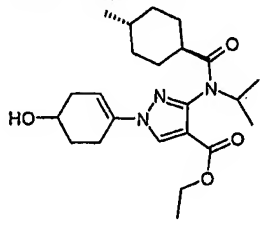
To a solution of Intermediate 7 (230 mg, 0.55 mmol) and potassium carbamate (450 mg, 3.3 mmol) in acetone (10 mL) was added 4-(chloromethyl)-1,3-thiazole (230 mg, 1.37 mmol) and the mixture heated under reflux for 16 hours under nitrogen. The solvent was removed *in vacuo,* the residue partitioned between DCM and water, the organic extract passed through a hydrophobic frit and concentrated. This was purified by SPE (silica), eluted with a gradient of ethyl acetate:cyclohexane (20-30%) to give the title compound.

MS calcd for $(C_{27}H_{34}N_4O_4S + H)^+$: 511

MS found (electrospray): $(M+H)^+ = 511$

Intermediate 151

Ethyl 1-(4-hydroxy-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylate



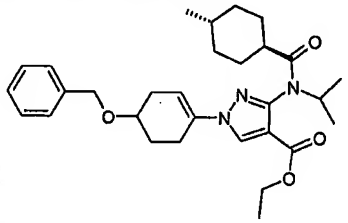
A solution of tetrabutyl ammonium fluoride in THF (1M, 1 mL, 1 mmol) was added a solution of Intermediate 140 (133 mg, 0.25 mmol) in THF (3 ml) at 0 °C under nitrogen. After 15 minutes, the mixture was allowed to attain room temperature and stirred for one hour. The mixture was poured into sodium bicarbonate solution (30 mL, 8% solution) and extracted with ethyl acetate (3 x 20 mL). The organic extract was dried (Na_2SO_4) and concentrated to give the title compound.

MS calcd for $(C_{23}H_{35}N_3O_4 + H)^+$: 418

MS found (electrospray): $(M+H)^+ = 418$

Intermediate 152

Ethyl 1-(4-benzyloxy-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylate



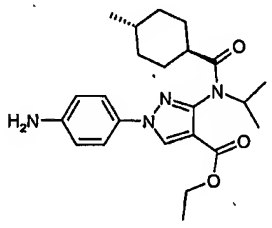
To a solution of Intermediate 151 (100mg, 0.24 mmol) in DMF (2 mL) under nitrogen was added sodium hydride (11 mg, 0.26 mmol, 60% dispersion in mineral oil). After effervescence ceased, benzyl bromide (28 ul, 0.24 mmol) was added dropwise. The mixture was stirred at room temperature for 24 hours, quenched by the addition of a few drops of water and ammonia, and the solvents evaporated *in vacuo*. The residue was partitioned between ethyl acetate and brine and the aqueous layer further extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4), concentrated and purified by SPE (silica), eluted with cyclohexane, then cyclohexane:DCM (3:1, then 1:1, then 1:3), then DCM and finally DCM/ethyl acetate to give the title compound.

MS calcd for $(C_{23}H_{35}N_3O_4 + H)^+$: 508

MS found (electrospray): $(M+H)^+ = 508$

Intermediate 153

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-aminophenyl}-1*H*-pyrazole-4-carboxylate



To a solution of Intermediate 56 (1.14g, 2.22 mmol) in dioxane (5 mL) was slowly added a solution of HCl in dioxane (4N, 10 mL) and the reaction stirred at room temperature for 16

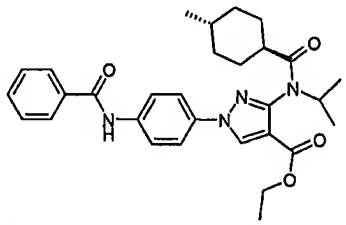
hours under nitrogen. A further portion of HCl in dioxane was added (10 mL) and stirring continued for 2 days. The solvents were evaporated and the mixture was partitioned between sodium bicarbonate solution (30 mL, 8% solution) and ethyl acetate and the aqueous layer further extracted with ethyl acetate (3 x 20 mL). The organic extract was dried (Na_2SO_4), evaporated, and purified by SPE (silica), eluted with DCM, then DCM:ethyl acetate (9:1, then 8:2) to give the title compound.

MS calcd for $(C_{23}H_{32}N_4O_3 + H)^+$: 413

MS found (electrospray): $(M+H)^+ = 413$

Intermediate 154

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylate



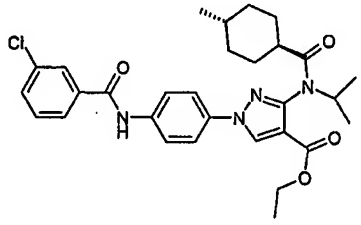
To a solution of Intermediate 153 (70 mg, 0.17 mmol) and ethyl diisopropylamine (30 ul, 0.17 mmol) in DCM (2 mL) under nitrogen, was added benzoyl chloride (20 ul, 0.17 mmol). After 2 hours, an 8% solution of sodium bicarbonate was added and the layers separated. The organic fraction was concentrated to give the title compound.

MS calcd for $(C_{30}H_{36}N_4O_4 + H)^+$: 517

MS found (electrospray): $(M+H)^+ = 517$

Intermediate 155

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(3-chlorophenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylate



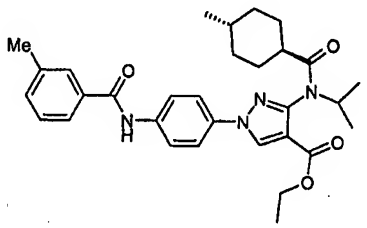
Prepared by a similar method to that described for Intermediate 154, replacing benzoyl chloride with 3-chloro benzoyl chloride. Purified by SPE (silica), eluted with DCM:cyclohexane (1:1), then DCM, then DCM:ethyl acetate (3:1), then then DCM:ethyl acetate (1:1) to give the title compound.

MS calcd for $(C_{30}H_{35}ClN_4O_4 + H)^+$: 551/553

MS found (electrospray): $(M+H)^+ = 551/553$

Intermediate 156

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(3-methylphenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylate



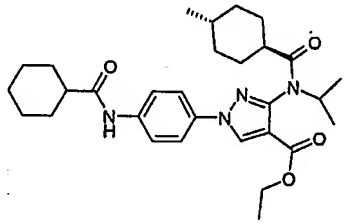
Prepared by a similar method to that described for Intermediate 154, replacing benzoyl chloride with 3-methyl benzoyl chloride. Purified by SPE (silica), eluted with DCM:cyclohexane (1:1), then DCM, then DCM:ethyl acetate (3:1), then DCM:ethyl acetate (1:1) to give the title compound.

MS calcd for $(C_{31}H_{38}N_4O_4 + H)^+$: 531

MS found (electrospray): $(M+H)^+ = 531$

Intermediate 157

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(4-cyclohexylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylate



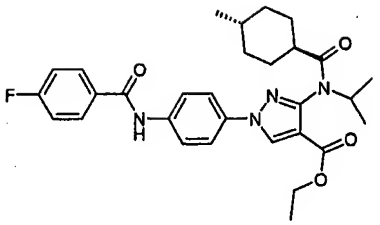
Prepared by a similar method to that described for Intermediate 154, replacing benzoyl chloride with cyclohexyl carbonyl chloride to give the title compound.

MS calcd for $(C_{30}H_{42}N_4O_4 + H)^+$: 523

MS found (electrospray): $(M+H)^+ = 523$

Intermediate 158

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(4-fluorophenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylate



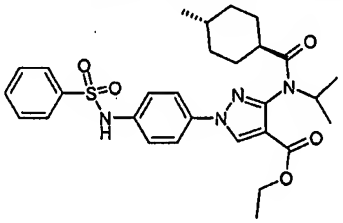
Prepared by a similar method to that described for Intermediate 154, replacing benzoyl chloride with 4-fluorobenzoyl chloride to give the title compound.

MS calcd for $(C_{30}H_{35}FN_4O_4 + H)^+$: 535

MS found (electrospray): $(M+H)^+$ = 535

Intermediate 159

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylsulfonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylate



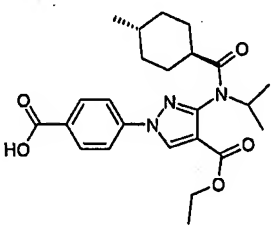
Prepared by a similar method to that described for Intermediate 154, replacing benzoyl chloride with phenyl sulfonyl chloride to give the crude title compound containing the di-sulfonylated product.

MS calcd for $(C_{29}H_{36}N_4O_5S + H)^+$: 553

MS found (electrospray): $(M+H)^+$ = 553

Intermediate 160

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(4-carboxy phenyl}-1*H*-pyrazole-4-carboxylate



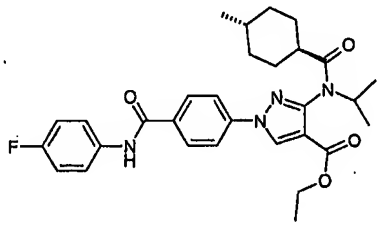
To a solution of Intermediate 57 in DCM (3 mL) was added TFA (3 mL) and the mixture stirred at room temperature for 16 hours. The solvent was evaporated *in vacuo* and the product purified by SPE (silica), eluted with cyclohexane, then DCM, then acetone, then methanol to give the title compound.

MS calcd for $(C_{24}H_{31}N_3O_5 + H)^+$: 442

MS found (electrospray): $(M+H)^+$ = check

Intermediate 161

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(4-fluorophenylamino)carbonyl]phenyl}-1*H*-pyrazole-4-carboxylate



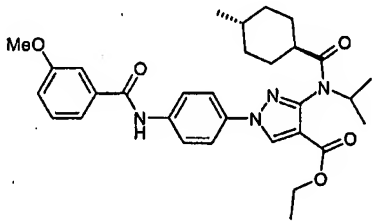
A solution of Intermediate 160 (74 mg, 0.17 mmol), HATU (76 mg, 0.20 mmol), and diisopropylethylamine (73 ul, 0.42 mmol) was stirred in dry DMF for 10 minutes. 4-Fluoroaniline (19 ul, 0.20 mmol) was added and the mixture stirred for 16 hours. The solvent was evaporated *in vacuo*, the residue dissolved in DCM and applied to a STRATA cartridge, eluted with DCM then methanol. Pooling and evaporation of the appropriate fractions afforded the title compound.

MS calcd for $(C_{30}H_{35}FN_4O_4 + H)^+$: 535

MS found (electrospray): $(M+H)^+ = 535$

Intermediate 162

Ethyl 3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(3-methoxyphenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylate



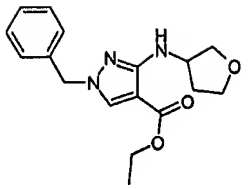
Prepared by a similar method to that described for Intermediate 154, replacing benzoyl chloride with 3-methoxy benzoyl chloride, to give the title compound.

MS calcd for $(C_{31}H_{38}N_4O_5 + H)^+$: 547

MS found (electrospray): $(M+H)^+ = 547$

Intermediate 163

Ethyl 1-(phenylmethyl)-3-[(tetrahydro-3-furanyl)amino]-1*H*-pyrazole-4-carboxylate.



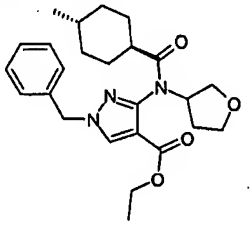
To a solution of ethyl 3-amino-1-(phenylmethyl)-1*H*-pyrazole-4-carboxylate (7.88 g, 32 mmol) and dihydro-3(2*H*)-furanone (1.60 g, 18.6 mmol) in DCM (100 mL) was added sodium triacetoxyborohydride (7.88 g, 37 mmol) and acetic acid (3.2 mL). The mixture was stirred for 16 hours, partitioned between DCM and saturated sodium bicarbonate solution and applied through a hydrophobic frit. The organic fraction was evaporated, the residue purified using a 330 g ISCO Flash column, eluting with a gradient of ethyl acetate in cyclohexane (5-60%) to give the title compound.

MS calcd for $(C_{17}H_{21}N_3O_3 + H)^+$: 316

MS found (electrospray): $(M+H)^+ = 316$

Intermediate 164

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-1-(phenylmethyl)-1*H*-pyrazole-4-carboxylate



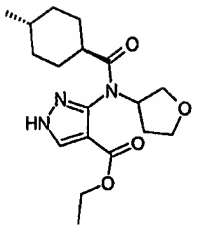
To a solution of Intermediate 163 (3.73 g, 11.8 mmol) in DCM (35 mL) was added *trans*-4-methylcyclohexanecarbonyl chloride (2.28 g, 14 mmol), followed by triethylamine (2.5 mL). The reaction was heated at 45 °C for 16 hours under nitrogen, whereupon further aliquots of triethylamine (2 mL) and *trans*-4-methylcyclohexanecarbonyl chloride (1.5 g) were added. Heating was continued for a further 16 hours. After cooling, the mixture was diluted with DCM, washed with hydrochloric acid solution (1M), then water, and then saturated sodium bicarbonate solution. The organic layer was passed through a hydrophobic frit, evaporated, and purified using 120 g ISCO Flash column, eluting with a gradient of ethyl acetate in cyclohexane (5-100%) to give the title compound.

MS calcd for $(C_{25}H_{33}N_3O_4 + H)^+$: 440

MS found (electrospray): $(M+H)^+ = 440$

Intermediate 165

Ethyl 3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-1*H*-pyrazole-4-carboxylate



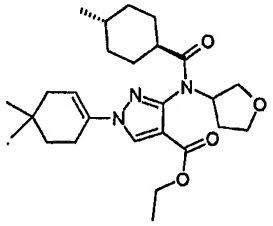
A mixture of Intermediate 164 (3.90 g, 8.88 mmol), 10% palladium on carbon (1.14 g, wet) and concentrated hydrochloric acid (2.5 mL) in ethanol (160 mL) was hydrogenated for 20 hours. The mixture was filtered through Celite, the solvent evaporated, and the residue purified using a 50 g SPE column, eluting with cyclohexane, then cyclohexane/ethyl acetate (3:1, 2:1, 1;1, 1:2, 1:3), then ethyl acetate. The crude product was dissolved in DCM and washed with sodium bicarbonate solution. The organic layer was passed through a hydrophobic frit and evaporated to give the title compound.

MS calcd for $(C_{18}H_{27}N_3O_4 + H)^+$: 350

MS found (electrospray): $(M+H)^+ = 350$

Intermediate 166

Ethyl 1-(4,4-dimethyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-3-furanyl)amino]-1*H*-pyrazole-4-carboxylate



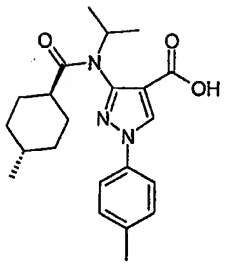
A mixture of Intermediate 165 (122 mg, 0.35 mmol), (4,4-dimethyl-1-cyclohexen-1-yl)boronic acid (107 mg, 0.7 mmol), copper (II) acetate (95 mg, 0.53 mmol) and pyridine (0.057 mL, 0.7 umol) in DCM (3 mL) was stirred in air for 18 hours. The mixture was filtered and the filtrate purified using Biotage silica column chromatography, eluting with ethyl acetate/cyclohexane (1:5), to give the title compound.

MS calcd for $(C_{26}H_{39}N_3O_4 + H)^+$: 458

MS found (electrospray): $(M+H)^+ = 458$

Example 1

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(4-methylphenyl)-1H-pyrazole-4-carboxylic acid



To Intermediate 6 (50 mg; 0.12 mmol) was added THF (1 mL), ethanol (1 mL) and 2M lithium hydroxide (1 mL; 2 mmol). The reaction was stirred at room temperature for 16 hrs.

The residue was purified by being partitioned between DCM and 2N hydrochloric acid, passed through a hydrophobic frit and the organic layer was concentrated to give the title compound. This purification protocol is **purification Method A**. When the product is not soluble in DCM, then ethyl acetate is employed as the organic solvent, the organic layer separated, dried (Na_2SO_4), and evaporated.

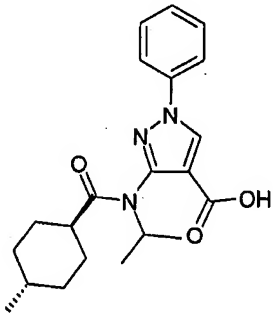
MS calcd for $(C_{22}H_{29}N_3O_3 + H)^+$: 384

MS found (electrospray): $(M+H)^+ = 384$

^1H NMR (CD_3OD) δ 8.79 (1H, s), 7.69 (2H, d), 7.35 (2H, d), 4.82 (1H, m), 2.40 (3H, s), 2.06 (1H, m), 1.79 (2H, d), 1.70-1.52 (3H, br), 1.43-1.18 (5H, br), 0.98 (3H, d), 0.78 (3H, d), 0.78-0.55 (2H, br) carboxylic acid proton not seen.

Example 2

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-phenyl-1*H*-pyrazole-4-carboxylic acid



A solution of Intermediate 2 (143 mg; 0.39 mmol) in tetrahydrofuran (1.5 mL), ethanol (1 mL) and water (0.5 mL) was treated with lithium hydroxide monohydrate (101 mg; 2.40 mmol) and stirred at room temperature overnight. The reaction mixture was concentrated to dryness and the residue partitioned between 2M HCl and dichloromethane. The organic layer was separated and dried (via a hydrophobic frit), and concentrated to dryness.

The residue was purified by reverse phase HPLC on a C18 column using a two-solvent gradient elution with (A) water containing formic acid (0.1%) and (B) acetonitrile-water (95:5 v/v) containing formic acid (0.05%), as the eluents and the detection method was mass spectroscopy using electrospray as the ionization method. Pooling and evaporation of the

appropriate fractions gave the title compound. This purification protocol is **purification Method B** (MDAP HPLC).

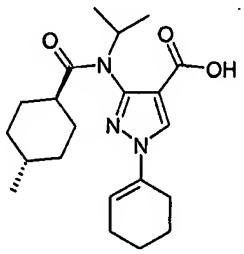
MS calcd for $(C_{21}H_{27}N_3O_3 + H)^+$: 370

MS found (electrospray): $(M+H)^+ = 370$

^1H NMR ($CDCl_3$): δ 8.57 (1H, s), 7.75 (2H, d), 7.54 (2H, t), 7.42 (1H, t), 4.98 (1H, m), 2.00 (1H, m), 1.71 (5H, m), 1.45 (1H, m), 1.30 (5H, m), 1.00 (2H, d), 0.77 (4H, d), 0.62 (1H, m) Carboxylic acid proton not seen.

Example 3

1-(1-Cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid



To Intermediate 52 (100 mg, 0.25 mmol) was added THF (2 mL), methanol (2 mL) and 2M lithium hydroxide (0.67 mL, 1.5 mmol). The reaction was stirred at room temperature overnight and the solvent removed.

The residue was purified by being acidified with 2N hydrochloric acid. The suspension added to a 1 g OASIS HLB cartridge, washed with water (3 column volumes) then eluted with methanol to give the title compound. This purification protocol is **purification Method C.**

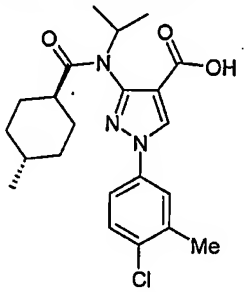
MS calcd for $(C_{21}H_{31}N_3O_3 + H)^+$: 374

MS found (electrospray): $(M+H)^+ = 374$

^1H NMR (d_6-DMSO) δ 8.49 (1H, s), 6.28 (1H, br), 4.68 (1H, m), 2.18 (2H, br), 1.88 (1H, br), 1.77 (2H, br), 1.67-1.38 (7H, br), 1.29-0.97 (5H,br), 0.82 (3H, d), 0.76 (3H, d), 0.68-0.43 (2H, br) plus 2 protons hidden under DMSO peak and carboxylic acid proton not seen.

Example 4

1-(4-Chloro-3-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid



Similarly prepared by the procedure described for Example 1 from Intermediate 37.

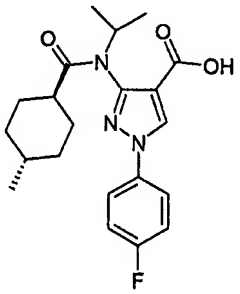
Subsequent to purification by Method A, further purification was achieved by dissolving the compound in dioxane, applying to an SPE column (NH_2) and eluting with dioxane then dioxane:acetic acid (9:1). This purification protocol is **purification Method D**.

MS calcd for $(C_{22}H_{28}ClN_3O_3 + H)^+$: 418/20

MS found (electrospray): $(M+H)^+$ = 418/20

Example 5

1-(4-Fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid



Similarly prepared by the procedure described for Example 1 from Intermediate 59.

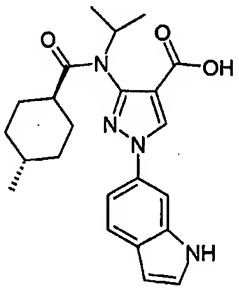
The crude product was purified using SPE (silica) column, eluted with DCM, then DCM:MeOH (6:1, then 4:1, then, 2:1, 1:1 and finally MeOH) to give the title compound. This purification protocol is **purification Method E**.

MS calcd for $(C_{23}H_{30}FN_3O_3 + H)^+$: 416

MS found (electrospray): $(M+H)^+$ = 416

Example 6

1-(6-Indolyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid



Similarly prepared by the procedure described for Example 1 from Intermediate 137.

The crude product was purified using ISCO Companion chromatography over silica, eluted with DCM, then DCM:MeOH (6:1, then 4:1, then 2:1 and finally 1:1) to give the title compound. This purification protocol is **purification Method F**.

MS calcd for $(C_{25}H_{32}N_4O_3 + H)^+$: 437

MS found (electrospray): $(M+H)^+$ = 437

The following compounds were made from the corresponding esters by a similar procedure to that described for Example 1, using an excess of lithium hydroxide. The method of purification (A, B, C, D, E or F) is given in the following Table.

Example 7
1-(4-Hydroxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 8
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylic acid

Example 9
1-[4-(Acetylamino)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 10
1-(4-Biphenylyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 11
1-[4-(Dimethylamino)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 12
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(methyloxy)phenyl]-1H-pyrazole-4-carboxylic acid
^{1}H NMR (CD_3OD) δ 8.70 (1H, s), 7.70 (2H, d), 7.05 (2H, d), 4.82 (1H, m), 3.86 (3H,s), 2.06 (1H, m), 1.79 (2H, d), 1.71-1.52 (3H, br), 1.42-1.15 (5H, br), 0.98 (3H, d), 0.78 (3H, d), 0.78-0.52 (2H, br) carboxylic acid not seen

Example 13
1-(4-Acetylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 14
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(trifluoromethyl)oxy]phenyl}-1H-pyrazole-4-carboxylic acid

Example 15
1-(4-Cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 16
1-{4-[(Dimethylamino)carbonyl]phenyl}-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 17
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3-thienyl)-1H-pyrazole-4-carboxylic acid

Example 18
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-4-carboxylic acid

Example 19
1-(3,5-Dimethylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 20
1-(3-Chloro-5-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 21
1-[3,5-Bis(trifluoromethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 22
1-(1,3-Benzodioxol-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 23
1-(2,3-Dihydro-1-benzofuran-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 24
1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 25
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3,4,5-trifluorophenyl)-1H-pyrazole-4-carboxylic acid

Example 26

1-(4-Chlorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD) δ 8.86 (1H, s), 7.82 (2H, d), 7.55 (2H, d), 4.81 (1H, m), 2.05 (1H, m), 1.78 (2H, br.d), 1.71-1.51 (3H, br), 1.40-1.18 (5H, br), 1.03-0.90 (3H, br.d), 0.80-0.75 (3H, d), 0.75-0.60 (2H, br) carboxylic acid proton not seen

Example 27

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[3-(methyloxy)phenyl]-1H-pyrazole-4-carboxylic acid

Example 28

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(methylsulfonyl)phenyl]-1H-pyrazole-4-carboxylic acid

Example 29

1-(2-Fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 30

1-(3-Hydroxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 31

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(3-methylphenyl)-1H-pyrazole-4-carboxylic acid

Example 32

1-(3-Fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD) δ 8.89 (1H, s), 7.68 (2H, m), 7.58 (1H, m), 7.15 (1H, t), 4.82 (1H, m), 2.05 (1H, m), 1.78 (2H, d), 1.62 (3H, br), 1.41-1.14 (5H, br), 0.99 (3H, br), 0.78 (3H, d), 0.78-0.62 (2H, br) carboxylic acid proton not seen

Example 33

1-(4-Aminophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 34

1-(3-Chlorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 35
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{3-[(trifluoromethyl)oxy]phenyl}-1H-pyrazole-4-carboxylic acid

Example 36
1-(4-Chloro-3-fluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 37
1-(3-Amino-4-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 38
1-(3-Fluoro-4-methylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid
^{1}H NMR (CD_3OD) δ 8.85 (1H, s), 7.56 (2H, d), 7.39 (1H, t), 4.82 (1H, m), 2.05 (1H, m), 1.78 (2H, d), 1.70-1.51 (3H, br), 1.40-1.15 (5H, br), 0.98 (3H, d), 0.77 (3H, d), 0.77-0.52 (2H, br) carboxylic acid not seen

Example 39
1-(3,4-Difluorophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 40
1-[(E)-1-Hexen-1-yl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 41
1-[(E)-2-Cyclohexylethenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 42
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[(E)-4-methyl-1-penten-1-yl]-1H-pyrazole-4-carboxylic acid

Example 43
1-[(E)-2-(4-Fluorophenyl)ethenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 44
1-(4-Ethenylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 45

1-[4-(Hydroxymethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 46

1-(4-Ethylphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD) δ 8.77 (1H, s), 7.69 (2H, d), 7.35 (2H, d), 4.79 (1H, m), 2.70 (2H, q), 2.05 (1H, m), 1.79 (2H, d), 1.68-1.51 (3H, br), 1.40-1.16 (8H, br), 0.98 (3H, d), 0.78 (3H, d), 0.78-0.52 (2H, br) carboxylic acid not seen

Example 47

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(1-methylethyl)phenyl]-1H-pyrazole-4-carboxylic acid

Example 48

1-(5-Acetyl-2-thienyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 49

1-(5-Chloro-2-thienyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 50

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(5-methyl-2-thienyl)-1H-pyrazole-4-carboxylic acid

Example 51

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-(5-phenyl-2-thienyl)-1H-pyrazole-4-carboxylic acid

Example 52

1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD): δ 8.40 (1H, s), 6.28 (1H, m), 4.63 (1H, m), 3.94-3.81 (2H, m), 3.47 (2H, m), 2.74-2.48 (2H, m), 2.35 (1H, m), 2.01-1.12 (16H, m), 1.05 (3H, d), 0.79 (3H, d), 0.75-0.53 (2H, m) Carboxylic acid proton is assumed to be exchanged with solvent.

Example 53

1-(6-Benzofuranyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 54

1-(Cyclohepten-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylic acid

Example 55

1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-(methylsulfonyl)-4-piperidinyl]amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD): δ 8.39 (1H, s), 6.28 (1H, m), 4.52 (1H, m), 3.74-3.61 (2H, m), 2.86-2.74 (2H, m), 2.79 (3H, s), 2.73-2.50 (2H, m), 2.35 (1H, m), 2.03-1.14 (16H excess, m), 1.05 (3H, d), 0.80 (3H, d), 0.76-0.52 (2H, m) Carboxylic acid proton is assumed to be exchanged with solvent.

Example 56

1-((4,4-Dimethyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD): δ 8.40 (1H, s), 6.24 (1H, m), 4.64 (1H, m), 3.96-3.81 (2H, m), 3.45 (2H, m), 2.59 (2H, m), 2.07 (2H, m), 1.97 (1H, m), 1.90-1.04 (14H, m), 1.01 (6H, s), 0.79 (3H, d), 0.75-0.54 (2H, m) Carboxylic acid proton is assumed to be exchanged with solvent

Example 57

1-(3-Chloro-4-benzyloxyphenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD): δ 8.77 (1H, s), 7.90 (1H, d), 7.71 (1H, dd), 7.50 (2H, d), 7.40 (2H, t), 7.33 (1H, t), 7.29 (1H, d), 5.25 (2H, s), 4.82 (1H, quintet), 2.05 (1H, m), 1.78 (2H, br d), 1.63 (2H, br m), 1.58 (1H, br m) 1.33(2H, m), 1.24 (3H, d), 0.98 (3H, d), 0.79 (3H, d), 0.66 (2H, br m) Carboxylic acid proton is assumed to be exchanged with solvent.

Example 58

1-(4-Benzyloxy-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1)-1H-pyrazole-4-carboxylic acid

Example 59

1-(4,4-Dimethyl)cyclohexen-1-yl)-3-{[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino}-1H-pyrazole-4-carboxylic acid

Example 60

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(E)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid

Example 61

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(Z)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid

Example 62

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(Z)-2-(3-pyrazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid

Example 63

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(E)-2-(3-pyrazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid

Example 64

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4[(E)-2-(tetrahydro-2H-pyran-4-yl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid

Example 65

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(E)-2-(4-thiazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD): δ 9.03 (1H, d), 8.88 (1H, s), 7.85 (2H, d), 7.74 (2H, d), 7.59 (1H, d), 7.50 (1H, d), 7.34 (1H, d), 4.68 (1H, m), 3.98-3.84 (2H, m), 3.49 (2H, m), 2.06 (1H, m), 1.94-1.23 (11H, m), 0.79 (3H, d), 0.75-0.55 (2H, m) Carboxylic acid proton is assumed to be exchanged with solvent.

Example 66

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(Z)-2-(4-thiazolyl)-ethenyl]phenyl}-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD): δ 8.95 (1H, d), 8.81 (1H, s), 7.77 (2H, d), 7.51 (2H, d), 7.32 (1H, d), 6.81 (1H, d), 6.76 (1H, d), 4.69 (1H, m), 3.91 (2H, m), 3.49 (2H, br. q), 2.08 (1H, m), 1.90-1.72 (5H, m), 1.70-1.51 (3H, m), 1.42-1.23 (3H, m), 0.79 (3H, d), 0.77-0.54 (2H, m). Carboxylic acid proton is assumed to be exchanged with solvent.

Example 67

1-((E)-2-*tert*-Butyl-ethenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

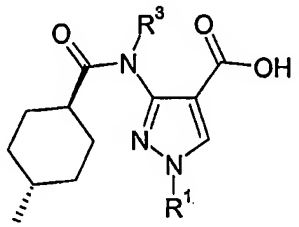
Example 68

1-((E)-2-Phenyl-ethenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 69

1-(4-Methyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (d_6-DMSO) δ 8.00 (1H, s), 6.08 (1H, br), 4.60 (1H, m), 2.52 (2H, br.q), 2.25 (1H, br), 1.99 (1H, br), 1.90-1.45 (7H, br), 1.42-1.29 (2H, br), 1.29-1.12 (2H,br), 1.12-0.88 (9H, br), 0.76 (3H, d), 0.65-0.38 (2H, br) carboxylic acid proton not seen.



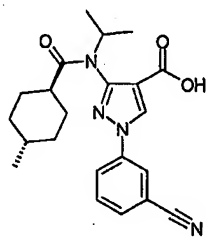
Ex. No.	Pre-cursor Inter-mediate Number	Purification method	Structure		Molecular Formula	Mass Spectrometry	
			R^1	R^3		$(M+H)^+$ Calcd	$(M+H)^+$ Found
7	7	A	-4-OH-Ph	iPr	$C_{21}H_{27}N_3O_4$	386	386
8	8	A	-4-CF_3-Ph	iPr	$C_{22}H_{26}F_3N_3O_3$	438	438
9	9	A	-4-NHAc-Ph	iPr	$C_{23}H_{30}N_4O_4$	427	427
10	10	A	-4-Ph-Ph	iPr	$C_{27}H_{31}N_3O_3$	446	446
11	11	A	-4-NMe_2-Ph	iPr	$C_{23}H_{32}N_4O_3$	413	413
12	12	A	-4-OMe-Ph	iPr	$C_{22}H_{29}N_3O_4$	400	400
13	13	A	4-Ac-Ph	iPr	$C_{23}H_{29}N_3O_4$	412	412
14	14	A	-4-OCF_3-Ph	iPr	$C_{22}H_{26}F_3N_3O_4$	454	454
15	15	A	4-CN-Ph	iPr	$C_{22}H_{26}N_4O_3$	395	395
16	16	B	4-$CONMe_2$-Ph	iPr	$C_{24}H_{32}N_4O_4$	441	441
17	17	C	3-thienyl	iPr	$C_{19}H_{25}N_3O_3S$	376	376
18	18	A	3-CF_3-Ph	iPr	$C_{22}H_{26}F_3N_3O_3$	438	438
19	19	D	3,5-di-Me-Ph	iPr	$C_{23}H_{31}N_3O_3$	398	398
20	20	D	3-Cl-5-F-Ph	iPr	$C_{21}H_{25}ClFN_3O_3$	422	422
21	21	D	3,5-di-CF_3-Ph	iPr	$C_{23}H_{25}F_6N_3O_3$	506	506
22	22	D	1,3-benzodioxol-5-yl	iPr	$C_{22}H_{27}N_3O_5$	414	414
23	23	D	2,3-dihydro-1-benzofuran-5-yl	iPr	$C_{23}H_{29}N_3O_4$	412	412
24	24	D	2,3-dihydro-1,4-benzodioxin-6-yl	iPr	$C_{23}H_{29}N_3O_5$	428	428
25	25	D	3,4,5-tri-F-Ph	iPr	$C_{21}H_{24}F_3N_3O_3$	424	424

26	26	A	4-Cl-Ph	iPr	$C_{21}H_{26}ClN_3O_3$	402/04	402/04
27	27	A	3-OMe-Ph	iPr	$C_{22}H_{29}N_3O_4$	400	400
28	28	A	4-$MeSO_2$-Ph	iPr	$C_{22}H_{29}N_3O_5S$	448	448
29	29	A	2-F-Ph	iPr	$C_{21}H_{26}FN_3O_3$	388	388
30	30	A	3-OH-Ph	iPr	$C_{21}H_{27}N_3O_4$	386	386
31	31	A	3-Me-Ph	iPr	$C_{22}H_{29}N_3O_4$	384	384
32	32	A	3-F-Ph	iPr	$C_{21}H_{26}FN_3O_3$	388	388
33	33	A	4-NH_2-Ph	iPr	$C_{21}H_{28}N_4O_3$	385	385
34	34	A	3-Cl-Ph	iPr	$C_{21}H_{26}ClN_3O_3$	402/04	402/04
35	35	A	3-OCF_3-Ph	iPr	$C_{22}H_{26}F_3N_3O_4$	454	454
36	36	A	3-F-4-Cl-Ph	iPr	$C_{22}H_{28}ClN_3O_3$	418/420	418/ 420
37	38	A	3-NH_2-4-Me-Ph	iPr	$C_{22}H_{30}N_4O_3$	399	399
38	39	A	3-F-4-Me-Ph	iPr	$C_{22}H_{28}FN_3O_3$	402	402
39	40	B	3,4-di-F-Ph	iPr	$C_{21}H_{25}F_2N_3O_3$	406	406
40	41	A	(E)-1-hexen-1-yl	iPr	$C_{21}H_{33}N_3O_3$	376	376
41	42	A	(E)-2-cyclohexylethenyl	iPr	$C_{23}H_{35}N_3O_3$	402	402
42	43	A	(E)-4-methyl-1-penten-1-yl	iPr	$C_{21}H_{33}N_3O_3$	376	376
43	44	A	(E)-2-(4-fluorophenyl)ethenyl	iPr	$C_{23}H_{28}FN_3O_3$	414	414
44	45	A	4-ethenylphenyl	iPr	$C_{23}H_{29}N_3O_3$	396	396
45	46	A	4-CH_2OH-Ph	iPr	$C_{22}H_{29}N_3O_3$	400	400
46	47	D	4-Et-Ph	iPr	$C_{23}H_{31}N_3O_3$	398	398
47	48	D	4-iPr-Ph	iPr	$C_{24}H_{33}N_3O_3$	412	412
48	61	D	5-Ac-2-thienyl	iPr	$C_{21}H_{27}N_3O_4S$	418	418
49	62	D	5-Cl-2-thienyl	iPr	$C_{19}H_{24}ClN_3O_3S$	410/12	410/12
50	63	D	5-Me-2-thienyl	iPr	$C_{20}H_{27}N_3O_3S$	390	390
51	64	D	5-Ph-2-thienyl	iPr	$C_{25}H_{29}N_3O_3S$	452	452
52	144	A	4-methyl-1-cyclohexen-1-yl	pyran-4-yl	$C_{24}H_{35}N_3O_4$	430	430
53	138	A	6-benzofuranyl	iPr	$C_{23}H_{27}N_3O_4$	410	410
54	143	A	cyclohepten-1-yl	pyran-4-yl	$C_{23}H_{27}N_3O_4$	430	430
55	146	A	4-methyl -1-cyclohexen-1-yl	1-Methyl sulfonyl-4-piperidinyl	$C_{25}H_{38}N_4O_5S$	507	507
56	142	A	4,4-dimethyl-cyclohexen-1-yl	pyran-4-yl	$C_{25}H_{37}N_3O_4$	444	444
57	55	A	3-Cl-4-BnO-Ph	iPr	$C_{28}H_{32}ClN_3O_4$	510/512	510/512
58	152	E	4-benzyloxy -1-cyclohexen-1-yl	iPr	$C_{28}H_{37}N_3O_4$	480	480
59	141	C	4,4-dimethyl -cyclohexen-1-yl	iPr	$C_{23}H_{35}N_3O_3$	402	402

60	99	B	4-([E]-Ph-ethenyl)Ph	pyran-4-yl	$C_{31}H_{35}N_3O_4$	514	514
61	99	B	4-([Z]-Ph-ethenyl)Ph	pyran-4-yl	$C_{31}H_{35}N_3O_4$	514	514
62	106	A	4-([Z]-(pyrazol-3-yl)ethenyl)Ph	iPr	$C_{26}H_{30}N_5O_4$	462	462
63	105	A	4-([E]-(pyrazol-3-yl)ethenyl)Ph	iPr	$C_{26}H_{30}N_5O_4$	462	462
64	107	A	4-([E]-(pyran-4-yl)ethenyl)Ph	iPr	$C_{28}H_{37}N_3O_4$	480	480
65	100	B	4-([E]-(1,3-thiazol-4-yl)ethenyl)Ph	pyran-4-yl	$C_{26}H_{32}N_4O_4S$	521	521
66	100	B	4-([Z]-(1,3-thiazol-4-yl)ethenyl)Ph	pyran-4-yl	$C_{26}H_{32}N_4O_5S$	521	521
67	58	D	(E)-2-tert-butylethenyl	iPr	$C_{21}H_{33}N_3O_3$	376	376
68	53	C	(E)-2-phenylethenyl	iPr	$C_{23}H_{29}N_3O_3$	396	396
69	126	C	4-Methyl-1-cyclohexen-1-yl	iPr	$C_{22}H_{33}N_3O_3$	387	387

Example 70

1-(3-Cyanophenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid



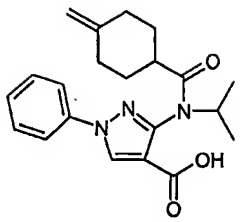
To 3-cyanophenylboronic acid (91 mg, 0.62 mmol) was added copper (II) acetate (85 mg, 0.55 mmol), Intermediate 66 (100 mg, 0.31 mmol) in dry THF (2 mL) and pyridine (50 uL, 0.62 mmol). The reaction was stirred at room temperature, in air for 16 hours. The solvent was removed and the residue purified by MDAP HPLC (purification method B) to give the title compound.

MS calcd for $(C_{22}H_{26}N_4O_3 + H)^+$: 395

MS found (electrospray): $(M+H)^+ = 395$

Example 71

3-{(1-Methylethyl)[(4-methylidenecyclohexyl)carbonyl]amino}-1-phenyl-1*H*-pyrazole-4-carboxylic acid



Intermediate 90 (122 mg, 0.31 mmol) was dissolved in THF (2 mL) and ethanol (2 mL). 2N sodium hydroxide solution (0.93 mL, 1.8 mmol) was added and the mixture stirred at room temperature for 2 days.

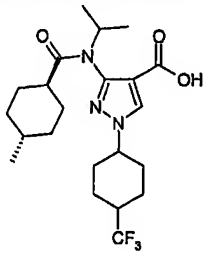
The residue was purified according to purification method A. Thus, the volatiles were removed *in vacuo* and the residue partitioned between 2N aqueous hydrochloric acid and ethyl acetate. The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated. The residue was triturated with ether to give the title compound.

MS calcd for $(C_{21}H_{25}N_3O_3 + H)^+$: 368

MS found (electrospray): $(M+H)^+ = 368$

Example 72

1-(4-Trifluoromethyl-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid



Similarly prepared by the procedure described for Example 71 from Intermediate 139.

The residue was purified according to purification method F. Thus, the volatiles were removed *in vacuo* and the residue partitioned between 2N aqueous hydrochloric acid and ethyl acetate. The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by SPE (silica) column, eluted with a gradient of ethyl acetate in cyclohexane (20% to 60%) to give the title compound.

MS calcd for $(C_{22}H_{34}F_3N_3O_3 + H)^+$: 442

MS found (electrospray): $(M+H)^+ = 442$

The following compounds were made from the corresponding esters by a similar procedure to that described for Example 71. The method of purification (A or B) is given in the following Table.

Example 73

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenyloxy)methyl]phenyl}-1*H*-pyrazole-4-carboxylic acid

^{1}H NMR ($CDCl_3$): 8.58 (1H, s), 7.76 (2H, d), 7.61 (2H, d), 7.32 (2H, m), 6.95 (3H, m), 5.15 (2H, s), 4.93 (1H, m), 2.00 (1H, m), 1.56-1.85 (5H, m), 1.24-1.48. (5H, m), 0.99 (3H, d), 0.78 (3H, d), 0.55-0.75 (2H, m). Carboxylic acid proton is assumed to be exchanged with moisture in the solvent.

Example 74

1-[4-(Phenylsulfonylmethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 75

1-[4-(Phenylthiomethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 76

1-[4-(Phenoxy)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 77

1-[4-{(1,3-Thiazol-4-ylmethyl)oxy}phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 78

1-[4-([E]-Phenylethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 79

1-[4-[Z]-Phenylethenyl))phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 80

1-[4-([E,Z]-(1,3-Thiazol-2-yl)ethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 81

1-[4-([E]-Phenyl-2-methylethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 82

1-[4-[E]-(Pyridin-4-yl)ethenyl))phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

^{1}H NMR (CD_3OD): δ 8.56 (1H, s), 8.46 (2H, d), 7.75 (2H, d), 7.67 (2H, d), 7.43 (2H, d), 7.35 (1H, d), 7.06 (1H, d), 4.81 (1H, s), 2.02-1.93 (1H, m), 1.80-1.65 (2H, m), 1.64-1.47 (3H, m),

1.40-1.11 (5H, m), 1.02-0.85 (3H, m), 0.72 (3H, d), 0.70-0.50 (2H, m) Carboxylic acid proton is assumed to be exchanged with solvent.

Example 83

1-[4-([E]-(1,3-Thiazol-4-yl)ethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

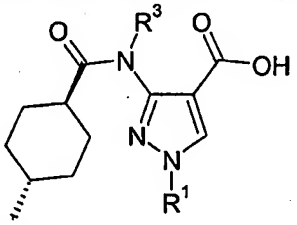
^{1}H NMR ($CDCl_3$): 8.93 (1H, d), 8.58 (1H, s), 7.76 (2H, d), 7.68 (2H, d), 7.56 (1H, d), 7.33 (1H, d), 7.23 (2H, d), 4.97 (1H, m), 2.00 (1H, m), 1.87-1.56 (4H, m), 1.24-1.50. (6H, m), 0.87-1.05 (3H, m), 0.78 (3H, d), 0.75-0.55 (2H, m). Carboxylic acid proton is assumed to be exchanged with moisture in the solvent.

Example 84

1-[4-([E]-(Furan-2-yl)ethenyl))phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

Example 85

1-[4-([E]-(2-Methyl-1,3-thiazol-4-yl)ethenyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid

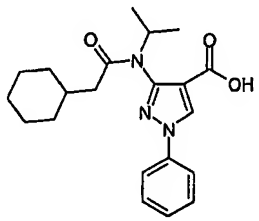


Example Number	Pre-cursor Inter-mediate Number	Purification method	Structure		Molecular Formula	Mass Spectrometry	
			R^1	R^3		$(M+H)^+$ Calcd	$(M+H)^+$ Found
73	149	B	4-PhOCH_2-Ph	iPr	$C_{28}H_{33}N_3O_4$	476	476
74	148	A	4-Ph-SO_2CH_2-Ph	iPr	$C_{28}H_{33}N_3O_5S$	524	524
75	147	B	4-Ph-SCH_2-Ph	iPr	$C_{28}H_{33}N_3O_3S$	492	492
76	54	A	4-PhO-Ph	iPr	$C_{27}H_{31}N_3O_4$	462	462
77	150	B	4-[(1,3-thiazol-4-ylmethyl)oxy]Ph	iPr	$C_{25}H_{30}N_4O_4S$	483	483
78	91	B	4-([E]-Ph-ethenyl)Ph	iPr	$C_{29}H_{33}N_3O_3$	472	472
79	91	B	4-([Z]-Ph-ethenyl)Ph	iPr	$C_{29}H_{33}N_3O_3$	472	472
80	93	A	4-([E,Z]-(1,3-thiazol-2-yl)ethenyl)Ph	iPr	$C_{26}H_{30}N_4O_3S$	479	479
81	94	B	4-([E]-Ph-2-methylethenyl)Ph	iPr	$C_{30}H_{35}N_3O_3$	486	486

82	95	B	4-([E]-(pyridin-4-yl)ethenyl)Ph	iPr	$C_{28}H_{32}N_4O_3$	473	473
83	96	B	4-([E]-(1,3-thiazol-4-yl)ethenyl)Ph	iPr	$C_{26}H_{30}N_4O_3S$	479	479
84	104	B	4-([E]-(furan-3-yl)ethenyl)Ph	iPr	$C_{27}H_{31}N_3O_4$	462	462
85	98	B	4-([E]-(2-methyl-1,3-thiazol-4-yl)ethenyl)Ph	iPr	$C_{27}H_{32}N_4O_3S$	493	493

Example 86

3-[(Cyclohexylacetyl)(1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 2 replacing Intermediate 2 with Intermediate 67. Purified by MDAP HPLC (purification method B) to give the title compound.

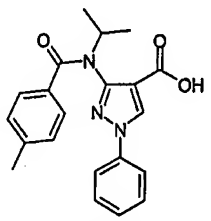
MS calcd for $(C_{21}H_{27}N_3O_3 + H)^+$: 370

MS found (electrospray): $(M+H)^+ = 370$

^1H NMR ($CDCl_3$): δ 8.58 (1H, s), 7.75 (2H, d), 7.54 (2H, t), 7.42 (1H, t), 5.01 (1H, m), 2.00 (2H, bm), 1.88 (1H, bm), 1.69 (2H, bm), 1.60 (2H, bm), 1.26 (5H, bm), 1.03 (5H, bm), 0.78 (2H, bm). Carboxylic acid proton not seen.

Example 87

3-{(1-Methylethyl)[(4-methylphenyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 2 replacing Intermediate 2 with Intermediate 68 to give the title compound.

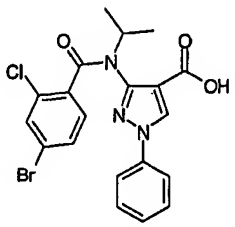
MS calcd for $(C_{21}H_{21}N_3O_3 + H)^+$: 364

MS found (electrospray): $(M+H)^+ = 364$

^1H NMR ($CDCl_3$): δ 8.58 (1H, s), 7.79 (2H, d), 7.52 (2H, t), 7.38 (1H, t), 7.25 (2H, d), 7.00 (2H, d), 4.82 (1H, m), 2.22 (3H, s), 1.25 (6H, d). Carboxylic acid proton not seen.

Example 88

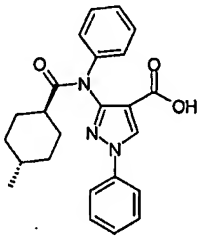
3-[[(4-Bromo-2-chlorophenyl)carbonyl](1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 69 to give the title compound.
MS calcd for $(C_{20}H_{17}BrClN_3O_3 + H)^+$: 460/2
MS found (electrospray): $(M+H)^+$ = 460/2

Example 89

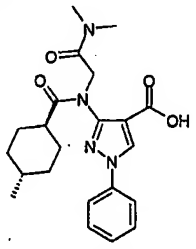
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](phenyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 71 to give the title compound.
MS calcd for $(C_{24}H_{25}N_3O_3 + H)^+$: 404
MS found (electrospray): $(M+H)^+$ = 404

Example 90

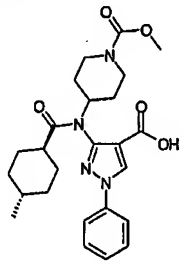
3-{[2-(Dimethylamino)-2-oxoethyl][(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 73 to give the title compound.
MS calcd for $(C_{22}H_{28}N_4O_4 + H)^+$: 413
MS found (electrospray): $(M+H)^+$ = 413

Example 91

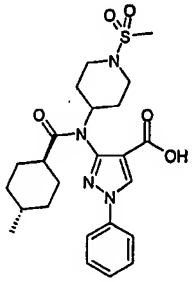
3-([(*trans*-4-Methylcyclohexyl)carbonyl]{1-[(methyloxy)carbonyl]-4-piperidinyl}amino)-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 80 to give the title compound.
MS calcd for $(C_{25}H_{32}N_4O_5 + H)^+$: 469
MS found (electrospray): $(M+H)^+ = 469$

Example 92

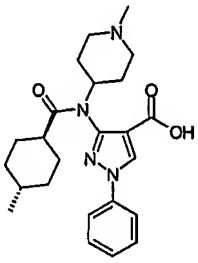
3-{[(*trans*-4-Methylcyclohexyl)carbonyl][1-(methylsulfonyl)-4-piperidinyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 81 to give the title compound.
MS calcd for $(C_{24}H_{32}N_4O_5S + H)^+$: 489
MS found (electrospray): $(M+H)^+ = 489$

Example 93

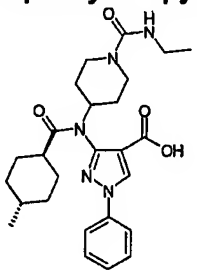
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methyl-4-piperidinyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 83 to give the title compound.
MS calcd for $(C_{24}H_{32}N_4O_3 + H)^+$: 425
MS found (electrospray): $(M+H)^+$ = 425
^1H NMR (CD_3OD) δ 8.91 (1H, s), 7.84 (2H, d), 7.55 (2H, t), 7.45 (1H, m), 4.75 (1H, m), 3.50 (2H, br), 3.17 (2H, br.t), 2.78 (3H, s), 2.22 (1H, br), 2.15-2.02 (3H, br), 1.77 (2H, br), 1.70-1.50 (4H, br), 1.40-1.25 (2H, br), 0.80 (3H, d), 0.80-0.55 (2H, br) carboxylic acid proton not seen.

Example 94

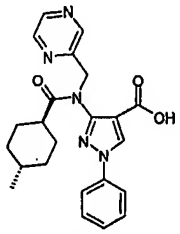
3-{{1-[(Ethylamino)carbonyl]-4-piperidinyl}[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 84 to give the title compound.
MS calcd for $(C_{26}H_{35}N_5O_4 + H)^+$: 482
MS found (electrospray): $(M+H)^+$ = 482

Example 95

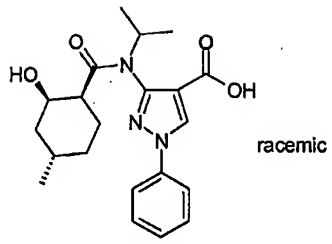
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](2-pyrazinylmethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 86 to give the title compound.
MS calcd for $(C_{23}H_{25}N_5O_3 + H)^+$: 420
MS found (electrospray): $(M+H)^+$ = 420

Example 96

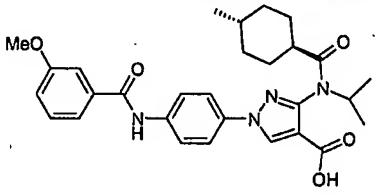
***rel*-3-[{[(1S,2R,4S)-2-Hydroxy-4-methylcyclohexyl]carbonyl}(1-methylethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid**



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 87 to give the title compound.
MS calcd for $(C_{21}H_{27}N_3O_4 + H)^+$: 386
MS found (electrospray): $(M+H)^+$ = 386

Example 97

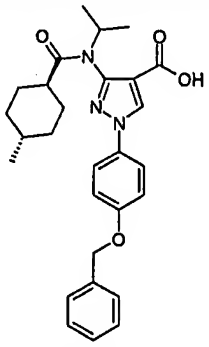
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(3-methoxyphenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 3 replacing Intermediate 52 with Intermediate 162 to give the title compound.
MS calcd for $(C_{29}H_{34}N_4O_5 + H)^+$: 519
MS found (electrospray): $(M+H)^+$ = 519

Example 98

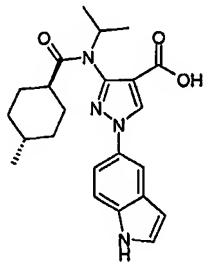
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylmethyl)oxy]phenyl}-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 71 replacing Intermediate 90 with Intermediate 49, and purified by MDAP HPLC to give the title compound.
MS calcd for $(C_{28}H_{33}N_3O_4 + H)^+$: 476
MS found (electrospray): $(M+H)^+$ = 476

Example 99

1-(1H-Indol-5-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 71 replacing Intermediate 90 with Intermediate 50 and purfied by method B to give the title compound.

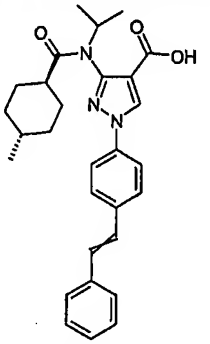
MS calcd for $(C_{23}H_{32}N_4O_3 + H)^+$: 409

MS found (electrospray): $(M+H)^+$ = 409

^{1}H NMR ($CDCl_3$) δ 8.63 (1H, br.s), 8.53 (1H, s), 7.95 (1H, s), 7.53 (2H, br.s), 7.36 (1H, t), 6.67 (1H, m), 4.99 (1H, m), 2.11-2.01 (1H, m), 1.92-1.56 (6H, m), 1.37-1.24 (5H, m), 1.06-0.98 (3H, m), 0.81-0.74 (4H, m) carboxylic acid proton not seen.

Example 100

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E/Z)-2-phenylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 71 replacing Intermediate 90 with Intermediate 91 to give the title compound.

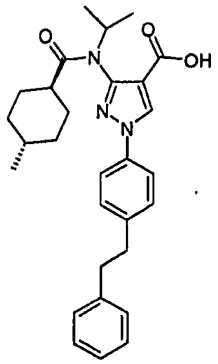
MS calcd for $(C_{29}H_{33}N_3O_3 + H)^+$: 472

MS found (electrospray): $(M+H)^+$ = 472

^{1}H NMR ($CDCl_3$) δ 8.58 (1H, s), 8.51 (1H, s), 7.74 (2H, d), 7.67 (2H, d), 7.61-7.53 (4H, m), 7.43-7.37 (4H, m), 7.34-7.24 (6H, m), 7.19 (1H, d), 7.14 (1H, d), 6.72 (1H, d), 6.61 (1H, d), 4.98 (2H, m), 2.05-1.93 (2H, m), 1.88-0.56 (36H, m) carboxylic acid proton not seen.

Example 101

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-(2-phenylethyl)phenyl]-1H-pyrazole-4-carboxylic acid



Example 100 (266 mg) in ethanol (10 mL) was subjected to atmospheric pressure hydrogenation with 10% palladium on carbon (60 mg, wet) for 3 hours. The reaction was filtered through Celite and concentrated.

The product was purified by silica flash column (20 g), eluted with a gradient of ethyl acetate in cyclohexane to give the title compound.

MS calcd for $(C_{29}H_{35}N_3O_3 + H)^+$: 474

MS found (electrospray): $(M+H)^+ = 474$

^1H NMR ($CDCl_3$) δ 8.55 (1H, s), 7.69-7.59 (2H, m), 7.39-7.16 (7H, m), 4.99 (1H, m), 3.09-2.90 (4H, m), 2.09-1.95 (1H, m), 1.90-0.55 (18H, m) carboxylic acid proton not seen.

The following compounds were prepared by a similar procedure to that described for Example 101.

Example 102

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[2-phenylethyl]phenyl}-1H-pyrazole-4-carboxylic acid

Example 103

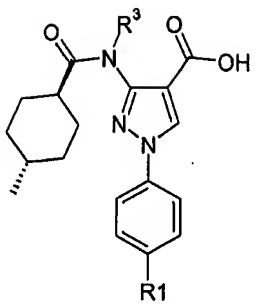
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[4-[(1,3-thiazol-4-yl)-ethyl]phenyl]-1H-pyrazole-4-carboxylic acid

^1H NMR ($CDCl_3$): 8.85 (1H, d), 8.52 (1H, s), 7.66 (2H, d), 7.45-7.25 (4H, m), 6.95 (1H, d), 4.97 (1H, m), 3.25-3.10 (4H, m), 2.00 (1H, m), 1.20-1.87 (7H, m), 0.87-1.10 (6H, m), 0.76 (3H, d), 0.75-0.55 (2H, m). Carboxylic acid proton is assumed to be exchanged with moisture in the solvent.

Example 104

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-{4-[(1,3-thiazol-4-yl)-ethyl]phenyl}-1H-pyrazole-4-carboxylic acid

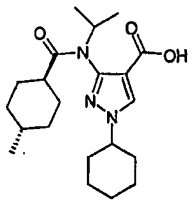
^1H NMR (CD_3OD): δ 8.96 (1H, s), 8.41 (1H, s), 7.64 (2H, d), 7.30 (2H, d), 7.16 (1H, d), 4.65 (1H, m), 3.97-3.81 (2H, m), 3.47 (2H, m), 3.18-3.05 (4H, m), 2.15 (1H, m), 2.0-1.21 (11H excess, m), 0.77 (3H, d), 0.74-0.52 (2H, m) Carboxylic acid proton is assumed to be exchanged with solvent



Example Number	Pre-cursor Example Number	Structure		Molecular Formula	Mass Spectrometry	
		R^1	R^3		$(M+H)^+$ Calcd	$(M+H)^+$ Found
102	Ex 61	PhCH2CH2	pyran-4-yl	$C_{31}H_{37}N_3O_4$	516	516
103	Ex 83	(1,3-thiazol-4-yl)-CH2CH2	iPr	$C_{26}H_{32}N_4O_3S$	481	481
104	Ex 66	(1,3-thiazol-4-yl)-CH2CH2	pyran-4-yl	$C_{28}H_{34}N_4O_4S$	523	523

Example 105

1-Cyclohexyl-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1H-pyrazole-4-carboxylic acid



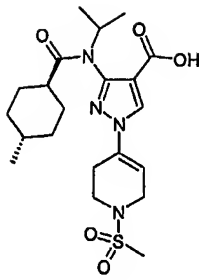
Example 3 (30 mg, 0.08 mmol) in ethanol (4 mL) was subjected to atmospheric pressure hydrogenation with 10% palladium on carbon, (wet, 10 mg) until hydrogen uptake had ceased. The reaction was filtered through Celite and concentrated to give the title compound.

MS calcd for $(C_{21}H_{33}N_3O_3 + H)^+$: 376

MS found (electrospray): $(M+H)^+ = 376$

Example 106

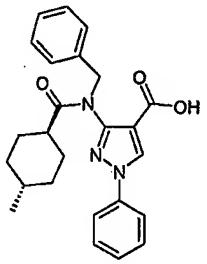
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-[1-(methylsulfonyl)-1,2,3,6-tetrahydro-4-pyridinyl]-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 3 replacing Intermediate 52 with Intermediate 111 to give the title compound.
MS calcd for $(C_{23}H_{36}N_4O_5S + H)^+$: 453
MS found (electrospray): $(M+H)^+ = 453$

Example 107

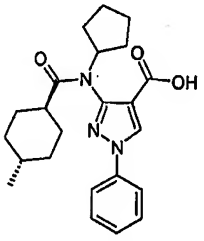
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](phenylmethyl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 1 replacing Intermediate 6 with Intermediate 127 to give the title compound.
MS calcd for $(C_{25}H_{27}N_3O_3 + H)^+$: 418
MS found (electrospray): $(M+H)^+ = 418$

Example 108

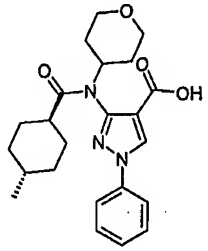
3-{Cyclopentyl[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 2 replacing Intermediate 2 with Intermediate 129 to give the title compound.
^{1}H NMR ($CDCl_3$) δ 8.56 (1H, s), 7.75 (2H, d), 7.55 (2H, t), 7.43 (1H, t), 4.91 (1H, m), 4.14 (1H, q), 2.11 (1H, br), 1.97 (1H, br), 1.85 (2H, br), 1.75-1.14 (11H, br), 0.77 (3H, d), 0.76-0.55 (2H, br) carboxylic acid proton not seen.

Example 109

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1-phenyl-1H-pyrazole-4-carboxylic acid

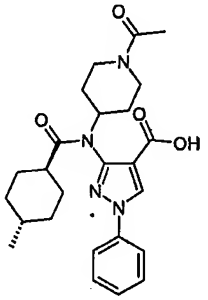


Prepared by a similar method to that described for Example 2 replacing Intermediate 2 with Intermediate 132 to give the title compound.

^{1}H NMR ($CDCl_3$) δ 8.57 (1H, s), 7.75 (2H, d), 7.55 (2H, t), 7.44 (1H, t), 4.88 (1H, m), 4.14 (2H, q), 4.02-3.87 (2H, br), 3.50 (2H, m), 2.05-1.55 (6H, br), 1.41-1.20 (5H, br), 0.78 (3H, d), 0.77-0.55 (2H, br) carboxylic acid proton not seen.

Example 110

3-{(1-Acetyl-4-piperidinyl)[(*trans*-4-methylcyclohexyl)carbonyl]amino}-1-phenyl-1H-pyrazole-4-carboxylic acid

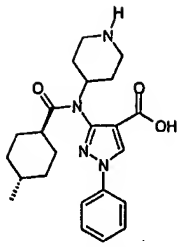


Prepared by a similar method to that described for Example 2 replacing Intermediate 2 with Intermediate 136 and purified by MDAP HPLC (purification method B) to give the title compound.

^{1}H NMR (CD_3OD) δ 8.80 (1H, s), 7.82 (2H, d), 7.55 (2H, t), 7.42 (1H, t), 4.71 (1H, br), 4.56 (1H, br), 3.94 (1H, br), 2.20 (1H, br), 2.65 (2H, br), 2.05-0.55 (19H, br) carboxylic acid proton not seen.

Example 111

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](4-piperidinyl)amino]-1-phenyl-1*H*-pyrazole-4-carboxylic acid

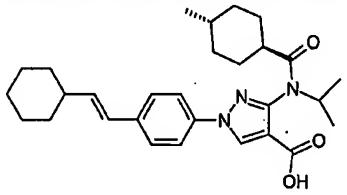


A solution of Example 121 (10 mg, 0.02 mmol, *supra*) in DCM (2 mL) and TFA (0.5 mL) was stirred at room temperature for 3 hours. The solvent was evaporated, and the residue purified by SPE (C18, reverse phase) to give the title compound.

^{1}H NMR (MeOD): δ 8.55 (1H, s), 7.80 (2H, m), 7.52 (2H, m), 7.38 (1H, m), 4.69 (1H, m), 3.35 (1H, m), 3.07 (2H, m), 12.18 (3H, m), 1.87 (3H, m), 1.25-1.64 (8H, m) 0.78 (3H, d), 0.56-0.74 (2H, m) Carboxylic acid proton is assumed to be exchanged with moisture in the solvent.

Example 112

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(E)-2-cyclohexylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid



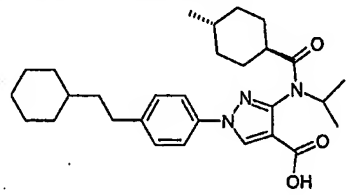
Intermediate 92 was treated with sodium hydroxide in a similar manner to that described in Example 71, and purified according to method A. A portion of this E/Z mixture (70 mg) was dissolved in dueterated chloroform (5 mL), a few crystals of iodine added and the mixture placed at room temperature for 2 days. DCM (20 mL) and sodium thiosulphate solution (20 mL) were added, the organic layer passed through a hydrophobic frit and evaporated to give the title compound.

MS calcd for $(C_{29}H_{39}N_3O_3 + H)^+$: 478

MS found (electrospray): $(M+H)^+ = 478$

Example 113

1-[4-(2-Cyclohexylethyl)phenyl]-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylic acid

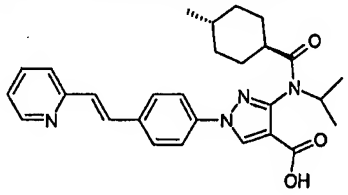


Intermediate 92 was treated with sodium hydroxide in a similar manner to that described in Example 71, and purified according to method A. A portion of this E/Z mixture was

hydrogenated using a similar procedure to that described for Example 101 to give the title compound.
MS calcd for $(C_{29}H_{41}N_3O_3 + H)^+$: 480
MS found (electrospray): $(M+H)^+$ = 480

Example 114

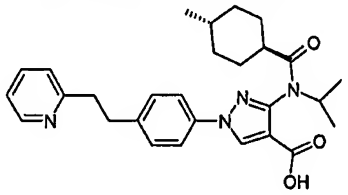
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[2-pyridinylethenyl]phenyl}-1H-pyrazole-4-carboxylic acid



Intermediate 97 was treated with sodium hydroxide and methanol in a similar manner to that described in Example 71, and purified according to method B. This E/Z mixture (108 mg) was dissolved in chloroform (40 mL), a few crystals of iodine (17 mg) added and the mixture placed at room temperature for 4 days. Sodium thiosulphate solution (50 mL) were added, the organic layer passed through a hydrophobic frit and evaporated to give the title compound.
MS calcd for $(C_{28}H_{32}N_4O_3 + H)^+$: 473
MS found (electrospray): $(M+H)^+$ = 473
^1H NMR ($CDCl_3$): δ 8.81 (1H, d), 8.66 (1H, s), 7.85-7.73 (5H, m), 7.66 (1H, d), 7.50 (1H, d), 7.27-7.21 (2H, m), 4.99 (1H, m), 2.04 (1H, m), 1.89-1.55 (5H, m), 1.53-1.20 (5H, m), 1.01 (3H, d), 0.77 (3H, d), 0.77-0.57 (2H, m). Carboxylic acid proton is assumed to be exchanged with moisture in the solvent.

Example 115

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[2-pyridinylethyl]phenyl}-1H-pyrazole-4-carboxylic acid

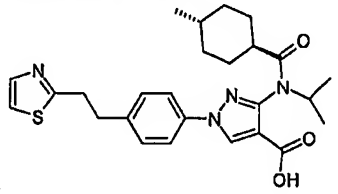


Intermediate 97 was treated with sodium hydroxide in a similar manner to that described in Example 71, and purified according to method B. A portion of this E/Z mixture was hydrogenated using a similar procedure to that described for Example 101 and purified by MDAP (purification method A) to give the title compound.
MS calcd for $(C_{28}H_{32}N_4O_3 + H)^+$: 475
MS found (electrospray): $(M+H)^+$ = 475

^{1}H NMR ($CDCl_3$): δ 8.67 (1H, d), 8.51 (1H, s), 8.13 (1H, br), 7.74-7.64 (2H, m), 7.41 (1H, d), 7.25 (1H, d), 7.21 (1H, d), 4.96 (1H, m), 3.20-3.09 (4H, m), 2.06-1.98 (1H, m), 1.86-1.29 (6H, m), 1.26 (3H, d), 1.00 (3H, d), 0.76 (3H, d), 0.75-0.52 (3H, m).

Example 116

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[1,3-thiazol-2-ylethyl]phenyl}-1H-pyrazole-4-carboxylic acid



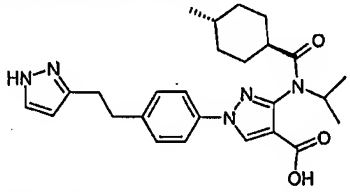
Intermediate 96 was treated with sodium hydroxide in a similar manner to that described in Example 71, and purified according to method B. A portion of this E/Z mixture was hydrogenated using a similar procedure to that described for Example 99 and purified by MDAP (purification method A) to give the title compound.

MS calcd for $(C_{26}H_{32}N_4O_3S + H)^+$: 481

MS found (electrospray): $(M+H)^+$ = 481

Example 117

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[2-(1*H*-pyrazol-3-yl)ethyl]phenyl}-1*H*-pyrazole-4-carboxylic acid



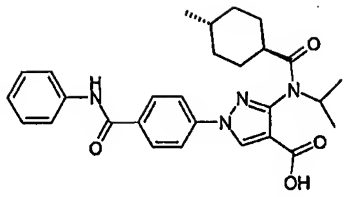
Intermediate 106 was treated with sodium hydroxide in a similar manner to that described in Example 71, and purified according to method A. A portion of this *cis* isomer was hydrogenated using a similar procedure to that described for Example 99, using a pressure of 25 psi, and purified by filtration through Celite to give the title compound.

MS calcd for $(C_{26}H_{33}N_5O_3 + H)^+$: 464

MS found (electrospray): $(M+H)^+$ = 464

Example 118

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylamino)carbonyl]phenyl}-1*H*-pyrazole-4-carboxylic acid



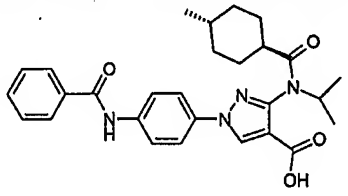
A solution of Intermediate 60 (35 mg, 0.07 mmol) and lithium iodide (46 mg, 0.35 mmol) in pyridine (1.5 mL) was heated at 120 °C for 2 days. A further portion of lithium iodide was added (46 mg) and heating continued for 3 days. The mixture was partitioned between ethyl acetate (20 mL) and dilute hydrochloric acid (10 mL, 2N), the aqueous layer extracted with ethyl actetate (2 x 10 mL), the combined organic fractions dried (Na_2SO_4) and evaporated. Purification was by SPE (silica), eluted with DCM, then EtOAc, then MeCN, then acetone, then acetone/MeOH, and finally MeOH to give the title compound.

MS calcd for $(C_{28}H_{32}N_4O_4 + H)^+$: 489

MS found (electrospray): $(M+H)^+ = 489$

Example 119

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 118 replacing Intermediate 60 with Intermediate 154 to give the title compound.

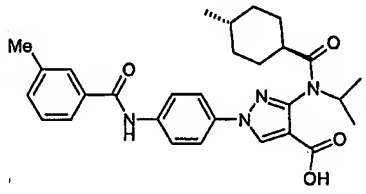
MS calcd for $(C_{28}H_{32}N_4O_4 + H)^+$: 489

MS found (electrospray): $(M+H)^+ = 489$

^1H NMR (DMSO): δ 12.8 (1H, br s), 10.35 (1H, s), 9.05 (1H, s), 7.88-8.0 (6H, m), 7.53-7.63 (3H, m), 4.73 (1H, m), 1.95 (1H, m), 1.20-1.80 (7H, m), 1.15 (3H, d), 0.88 (3H, d), 0.75 (3H, d), 0.45-0.70 (2H, m)

Example 120

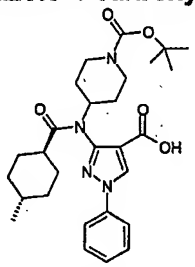
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(3-methylphenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 3 replacing Intermediate 52 with Intermediate 156, and using ethanol in place of methanol, to give the title compound.
MS calcd for $(C_{29}H_{34}N_4O_4 + H)^+$: 503
MS found (electrospray): $(M+H)^+$ = 503
^{1}H NMR (DMSO): δ 13.00 (1H, br s), 10.40 (1H, s), 9.05 (1H, s), 7.75-7.97 (6H, m), 7.40-7.45 (2H, m), 4.73 (1H, m), 2.42 (3H, s), 1.95 (1H, m), 1.15-1.70 (7H, m), 1.15 (3H, br d), 0.75 (3H, br), 0.50-0.70 (2H, m)

Example 121

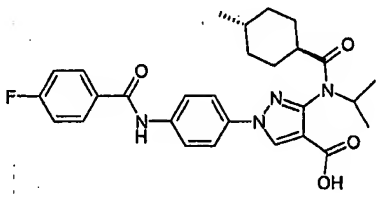
3-([(*trans*-4-Methylcyclohexyl)carbonyl]{1-[(*tert*-butyloxy)carbonyl]-4-piperidinyl}amino)-1-phenyl-1H-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 5 replacing Intermediate 59 with Intermediate 76 to give the title compound.
MS calcd for $(C_{28}H_{38}N_4O_5 + H)^+$: 511
MS found (electrospray): $(M+H)^+$ = 511

Example 122

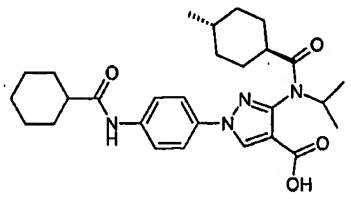
3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(4-fluorophenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 3 replacing Intermediate 52 with Intermediate 158, and using ethanol in place of methanol, and purified by MDAP to give the title compound.
MS calcd for $(C_{28}H_{31}FN_4O_4 + H)^+$: 507
MS found (electrospray): $(M+H)^+$ = 507
^{1}H NMR (DMSO): δ 12.80 (1H, br s), 10.45 (1H, s), 9.03 (1H, s), 8.07 (2H, m), 7.92 (4H, m), 7.40 (2H, m), 4.73 (1H, m), 1.95 (1H, m), 1.05-1.70 (7H, m), 1.15 (3H, br d), 0.88 (3H, br d), 0.75 (3H, d), 0.45-0.70 (2H, m)

Example 123

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(cyclohexylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid



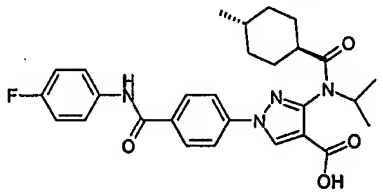
Prepared by a similar method to that described for Example 3 replacing Intermediate 52 with Intermediate 157 to give the title compound.

MS calcd for $(C_{30}H_{38}N_4O_4 + H)^+$: 495

MS found (electrospray): $(M+H)^+ = 495$

Example 124

1-(4-{[(4-Fluorophenyl)amino]carbonyl}phenyl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylic acid



Prepared by a similar method to that described for Example 3 replacing Intermediate 52 with Intermediate 161 to give the title compound.

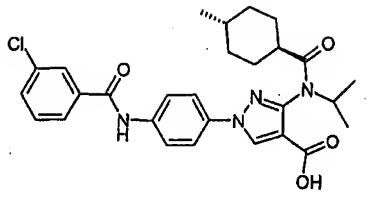
MS calcd for $(C_{28}H_{31}FN_4O_4 + H)^+$: 507

MS found (electrospray): $(M+H)^+ = 507$

^{1}H NMR (d_6-DMSO): δ 12.95 (1H, s), 10.40 (1H, s), 9.26 (1H, s), 8.15 (2H, d), 8.08 (2H, t), 7.81 (2H, quart), 7.22 (2H, t), 4.75 (1H, quint), 1.92-1.97 (1H, m), 1.62-1.68 (2H, m), 1.45-1.52 (3H, m), 1.19-1.27 (2H, m), 1.17 (3H, d), 0.88 (3H, d), 0.74 (3H, d), 0.50-0.68 (2H, m).

Example 125

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{3-[(chlorophenylcarbonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid



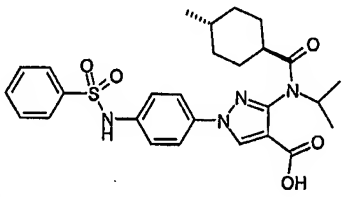
Prepared by a similar method to that described for Example 3 replacing Intermediate 52 with Intermediate 155 to give the title compound.

MS calcd for $(C_{28}H_{31}ClN_4O_4 + H)^+$: 523/25

MS found (electrospray): $(M+H)^+$ = 523/25

Example 126

3-[[(*trans*-4-Methylcyclohexyl)carbonyl](1-methylethyl)amino]-1-{4-[(phenylsulfonyl)amino]phenyl}-1*H*-pyrazole-4-carboxylic acid



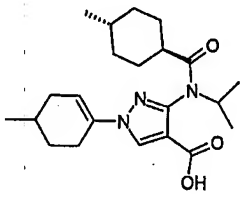
Prepared by a similar method to that described for Example 3 replacing Intermediate 52 with Intermediate 159 to give the title compound.

MS calcd for $(C_{27}H_{32}N_4OS + H)^+$: 525

MS found (electrospray): $(M+H)^+$: 525

Example 127

Enantiomer A of 1-(4-methyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylic acid



homochiral

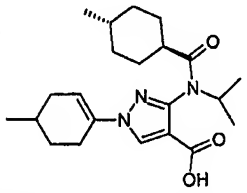
The enantiomers of Example 69 were separated using a chiralpak AD column, eluted with n-heptane:ethanol (95:5) containing 0.1% TFA. Enantiomer A eluted first with a retention time of 15.8 minutes.

^{1}H NMR (DMSO): δ 12.60 (1H, br), 8.00 (1H, s), 6.27 (1H, br m), 4.68 (1H, m), 2.60 (1H, m), 2.28 (1H, br d), 1.15-1.90 (13H, m), 1.09 (3H, d), 0.95 (3H, d), 0.81 (3H, d), 0.75 (3H, d), 0.45-0.70 (2H, m)

The ^{1}H NMR was identical with that of Example 128.
MS calcd for $(C_{22}H_{33}N_3O_3 + H)^+$: 388
MS found (electrospray): $(M+H)^+$: 388

Example 128

Enantiomer B of 1-(4-methyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](1-methylethyl)amino]-1*H*-pyrazole-4-carboxylic acid

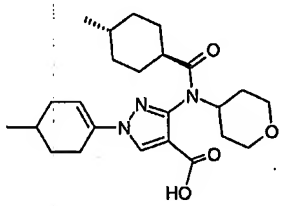


homochiral

The enantiomers of Example 69 were separated using a chiralpak AD column, eluted with n-heptane:ethanol (95:5) containing 0.1% TFA. Enantiomer B eluted second with a retention time of 17.6 minutes.
The ^{1}H NMR was identical with that of Example 127.
MS calcd for $(C_{22}H_{33}N_3O_3 + H)^+$: 388
MS found (electrospray): $(M+H)^+$: 388

Example 129

Enantiomer A of 1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylic acid



homochiral

Step 1:
The enantiomers of Intermediate 144 were separated using a 2 cm Chiralpak AD column, eluted with [n-heptane:IPA (95:5)], mixed fractions being re-processed as required. Enantiomer A eluted first. Pooling and evaporation of the fractions gave Enantiomer A of ethyl 1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate.

Chiral purity >99% e.e. with a retention time of 40.3 min., Analytical Chiralpak AD-H column, eluted with [n-heptane:IPA (97:3)] flow rate 1ml/min.
MS calcd for $(C_{26}H_{39}N_3O_4 + H)^+$: 458
MS found (electrospray): $(M+H)^+$: 458

Step 2:

Enantiomer A of ethyl 1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl) carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate was deprotected using sodium hydroxide in a similar manner to that described in Example 71, to give the title compound.

^{1}H NMR ($CDCl_3$): δ 8.17 (1H, s), 6.26 (1H, m), 4.80 (1H, m), 4.01-3.83 (2H, m), 3.55-3.40 (2H, m), 2.69-2.44 (2H, m), 2.40-2.28 (1H, m), 2.00-1.17 (16H excess, m), 1.06 (3H, d), 0.79 (3H, d), 0.76-0.55 (2H, m) Carboxylic acid proton not seen

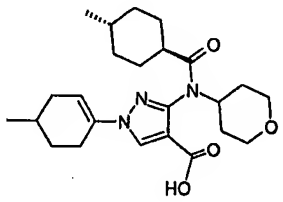
The ^{1}H NMR spectrum was identical with that of Example 130.

MS calcd for $(C_{24}H_{35}N_3O_4 + H)^+$: 430

MS found (electrospray): $(M+H)^+$: 430

Example 130

Enantiomer B of 1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylic acid



homochiral

Step 1:

The enantiomers of Intermediate 144 were separated using a 2 cm Chiralpak AD column, eluted with [n-heptane:IPA (95:5)], mixed fractions being re-processed as required. Enantiomer B eluted second. Pooling and evaporation of the fractions gave Enantiomer B of ethyl 1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl)carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate.

Chiral purity >99% e.e. with a retention time of 41.7 min., Analytical Chiralpak AD-H column, eluted with [n-heptane:IPA (97:3)] flow rate 1ml/min.

MS calcd for $(C_{26}H_{39}N_3O_4 + H)^+$: 458

MS found (electrospray): $(M+H)^+$: 458

Step 2:

Enantiomer B of ethyl 1-((4-Methyl)cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl) carbonyl](tetrahydro-2H-pyran-4-yl)amino]-1H-pyrazole-4-carboxylate was deprotected using sodium hydroxide in a similar manner to that described in Example 71, to give the title compound.

^{1}H NMR ($CDCl_3$): δ 8.17 (1H, s), 6.26 (1H, m), 4.80 (1H, m), 4.01-3.83 (2H, m), 3.55-3.40 (2H, m), 2.69-2.44 (2H, m), 2.40-2.28 (1H, m), 2.00-1.17 (16H excess, m), 1.06 (3H, d), 0.79 (3H, d), 0.76-0.55 (2H, m) Carboxylic acid proton not seen

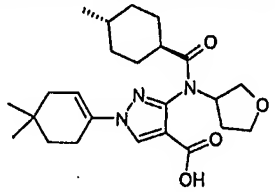
The ^{1}H NMR spectrum was identical with that of Example 129.

MS calcd for $(C_{24}H_{35}N_3O_4 + H)^+$: 430

MS found (electrospray): $(M+H)^+$: 430

Example 131

1-(4,4-Dimethyl-1-cyclohexen-1-yl)-3-[[(*trans*-4-methylcyclohexyl) carbonyl](tetrahydro-3-furanyl)amino]-1*H*-pyrazole-4-carboxylic acid



To a solution of Intermediate 166 (75 mg, 0.16 mmol) in THF (1.0 mL) and methanol (1.0 mL) was added sodium hydroxide solution (0.5 mL, 2N). The mixture was stirred for 24 hours, DCM added and the organic fraction washed with hydrochloric acid solution. The organic layer was passed through a hydrophobic frit and the solvent evaporated to give the title compound.

MS calcd for $(C_{24}H_{35}N_3O_4 + H)^+$: 430

MS found (electrospray): $(M+H)^+ = 30$

^{1}H NMR (CD_3OD): δ 8.35 (1H, s), 6.20 (1H, dd), 5.13-4.93 (1H, m), 4.03-3.50 (4H, m), 2.55 (2H, br s), 2.25-1.25 (14H, m), 1.10 (6H, s), 0.75-0.52 (2H, m), 0.78 (3H, d) carboxylic acid proton not seen.

The chemical entities according to the invention may be formulated for administration in any convenient way, and the invention therefore also includes within its scope pharmaceutical compositions for use in therapy, comprising a compound of formula (I) or a physiologically acceptable salt or solvate thereof in admixture with one or more physiologically acceptable diluents or carriers.

The chemical entities of the present invention can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical, transdermal, or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the chemical entities can be formulated into conventional oral dosage forms such as capsules, tablets and liquid preparations such as syrups, elixirs and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the chemical entities of the

invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the chemical entities may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various chemical entities to be administered can be determined by standard procedures taking into account factors such as the compound (IC_{50}) potency, (EC_{50}) efficacy, and the biological half-life (of the chemical entity), the age, size and weight of the patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for chemical entities with low oral bioavailability, relatively higher doses will have to be administered. Oral administration is a preferred method of administration of the present chemical entities.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula(I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

Chemical entities of Formula (I) which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil. olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional non-CFC propellant such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

ASSAY

The potential for chemical entities of the invention to inhibit NS5B wildtype HCV polymerase activity may be demonstrated, for example, using the following *in vitro* assay:

In Vitro Detection of inhibitors of HCV RNA-dependent RNA Polymerase Activity

Incorporation of [^{33}P]-GMP into RNA was followed by absorption of the biotin labelled RNA polymer by streptavidin containing SPA beads. A synthetic template consisting of biotinylated 13mer-oligoG hybridised to polyrC was used as a homopolymer substrate.

Reaction Conditions were 0.5 μM [^{33}P]-GTP (20 Ci/mMol), 1 mM Dithiothreitol, 20 mM $MgCl_2$, 5mM $MnCl_2$, 20 mM Tris-HCl, pH7.5, 1.6 μg/mL polyC/0.256 μM biotinylated oligoG13, 10% glycerol, 0.01% NP-40, 0.2 u/μL RNasin and 50 mM NaCl.

HCV RNA Polymerase (Recombinant full-length NS5B (Lohmann et al, J. Virol. 71 (11), 1997, 8416 'Biochemical properties of hepatitis C virus NS5B RNA-dependent RNA polymerase and identification of amino acid sequence motifs essential for enzymatic activity') expressed in baculovirus and purified to homogeneity) was added to 4 nM final concentration.

5x concentrated assay buffer mix was prepared using 1M $MnCl_2$ (0.25 mL), glycerol (2.5mL), 10% NP-40 (0.025 mL) and Water (7.225 mL), *Total* 10 mL.

2x concentrated enzyme buffer contained 1M-Tris-HCl, pH7.5 (0.4 mL), 5M NaCl (0.2 mL), 1M-$MgCl_2$ (0.4 mL), glycerol (1 mL), 10% NP-40 (10 μL), 1M DTT (20 μL) and water (7.97 mL), *Total* 10 mL.

Substrate Mix was prepared using 5x Concentrated assay Buffer mix (4μL), [^{33}P]-GTP (10 μCi/μL, 0.02μL), 25 μM GTP (0.4 μL), 40 u/μL RNasin (0.1 μL), 20 μg/mL polyrC/biotinylated-oligorG (1.6 μL), and Water (3.94 μL), *Total* 10 μL.

Enzyme Mix was prepared by adding 1mg/ml full-length NS5B polymerase (1.5 μL) to 2.81mL 2x-concentrated enzyme buffer.

The Assay was set up using compound (1μL), Substrate Mix (10 μL), and Enzyme Mix (added last to start reaction) (10 μL), *Total* 21 μL.

The reaction was performed in a U-bottomed, white, 96-well plate. The reaction was mixed on a plate-shaker, after addition of the Enzyme, and incubated for 1h at 22°C. After this time, the reaction was stopped by addition of 40 μL 1.875 mg/ml streptavidin SPA beads in 0.1 M EDTA. The beads were incubated with the reaction mixture for 1h at 22°C after which 120 μL 0.1 M EDTA in PBS was added. The plate was sealed, mixed centrifuged and incorporated radioactivity determined by counting in a Trilux (Wallac) or Topcount (Packard) Scintillation Counter.

After subtraction of background levels without enzyme, any reduction in the amount of radioactivity incorporated in the presence of a compound, compared to that in the absence, was taken as a measure of the level of inhibition. Ten concentrations of compounds were tested in three- or fivefold dilutions. From the counts, percentage of inhibition at highest concentration tested or IC_{50}s for the compounds were calculated using Grafit3, Grafit4 or Grafit5 software packages or a data evaluation macro for Excel based on XLFit software (IDBS).

The exemplified compounds had an IC_{50} of <80μM in the above described assay. In one aspect, compounds have an IC_{50} of <35μM. In another aspect, compounds have an IC_{50} of <5μM; in yet another aspect, compounds have an IC_{50} of <1μM. Accordingly, the compounds of the invention are of potential therapeutic benefit in the treatment and prophylaxis of HCV.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example immune therapies (eg. Interferon, such as Interferon alfa-2a (Roferon-A; Hoffmann-La Roche), inteferon alpha-2b (Intron-A; Schering-Plough), interferon alfacon-1 (Infergen; Intermune), peginterferon alpha-2b (Peg-Intron; Schering-Plough) or peginterferon alpha-2a (Pegasys; Hoffmann-La Roche)), therapeutic vaccines, antifibrotic agents, anti-inflammatory agents such as corticosteroids or NSAIDs, bronchodilators such as beta-2 adrenergic agonists and xanthines (e.g. theophylline), mucolytic agents, anti-muscarinics, anti-leukotrienes, inhibitors of cell adhesion (e.g. ICAM antagonists), anti-oxidants (eg N-acetylcysteine), cytokine agonists, cytokine antagonists, lung surfactants and/or antimicrobial and anti-viral agents (eg ribavirin and amantidine). The compositions according to the invention may also be used in combination with gene replacement therapy.

The invention thus provides, in a further aspect, a combination comprising at least one compound of formula (I) or a physiologically acceptable salt or solvate thereof together with at least one other therapeutically active agent, especially interferon and/or ribavirin.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

All publications, including but not limited to patents and patent applications cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference as though fully set forth.